Depressive symptoms in patients with schizophrenia

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DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

COUNT SYMPTOMS THAT COUNT

Proefschrift

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General introduction

THE ETIOLOGY AND COURSE OF DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

Schizophrenia is a psychiatric disease with severe consequences for mental health and social functioning. For most patients schizophrenia is a chronic disease, yet some of them may recover substantially from their (social) disabilities.[1,2] Patients with schizophrenia tend to hear voices and have delusional ideas (positive symptoms), suffer from inability to experience pleasure (anhedonia) and social withdrawal (negative symptoms).[3] Depressive symptoms are also common among patients with schizophrenia. About 40% of the patients have sub-syndromal depressive symptoms, as they meet two to four symptoms of depression.[4,5] Sub-syndromal depressive symptoms may lead to a diagnosis of depression, which is prevalent among 25% of the patients.[6,7]

Depressive symptoms are associated with a high burden of disease and low quality of life.[8] Patients with depressive symptoms may have a higher risk of psychotic relapse, hospitalization and higher health care costs.[9-11] Depressive symptoms are associated with poor outcome on recovery and reintegration into the community.[12] The risk of suicide or suicidal attempts is also elevated in patients with schizophrenia and depressive symptoms.[13-16]

Patients may experience depressive symptoms throughout all phases of illness,[17,18] and the prevalence of depressive symptoms is independent from the duration of illness.[19] Depressive symptoms can be intrinsic to schizophrenia and occur during acute psychosis,[20] or they can be a prodromal sign for an upcoming psychotic episode.[21] In patients with remitted psychotic symptoms, depressive symptoms may represent demoralization syndrome or post-psychotic depression. Demoralization syndrome can be explained as a psychological state in reaction to an uncontrollable life event (the psychosis) which jeopardizes the patients' prospects. Post-psychotic depression is the term for diagnosis of a depression following a psychotic episode. In contrast to post-psychotic depression, patients with demoralization syndrome often lack the biological symptoms of depression. They are able to enjoy the present and become activated when they are motivated.[22]

Recognition of depressive symptoms is complicated in patients with schizophrenia because the DSM-IV diagnostic criteria for a major depressive episode (MDE) overlap with negative symptoms.[6,23-25] For example, flattened affect is also a negative symptom. Furthermore, depressive symptoms overlap with other psychotic symptoms, e.g. feelings of guilt can be part of a delusion.[26] The clinician should further consider that depressive symptoms can occur as part of a differential diagnosis other than (post psychotic) depression (Figure 1). Depressive symptoms can also be a side effect from antipsychotics. They may occur as part of drug-induced akathesia or parkinsonian effects, without the observable (motor) extrapyramidal symptoms (EPS).[25] Other organic factors which can induce depressive symptoms are substance abuse or sudden withdrawal of illicit drugs or alcohol.[20,27] Another complicating factor is that depressive symptoms can be indistinguishable if patients suffer from depressive symptoms, negative symptoms and/or extrapyramidal symptoms (EPS) at the same time (Figure 2). The following case illustrates the complexity of diagnosing a patient with schizophrenia and depressive symptoms in clinical practice.

FIGURE 1. Scheme for differential diagnoses of depressive symptoms in patients with psychotic symptoms in remission, adapted from Hausmann and Fleischhacker (2002).[27]

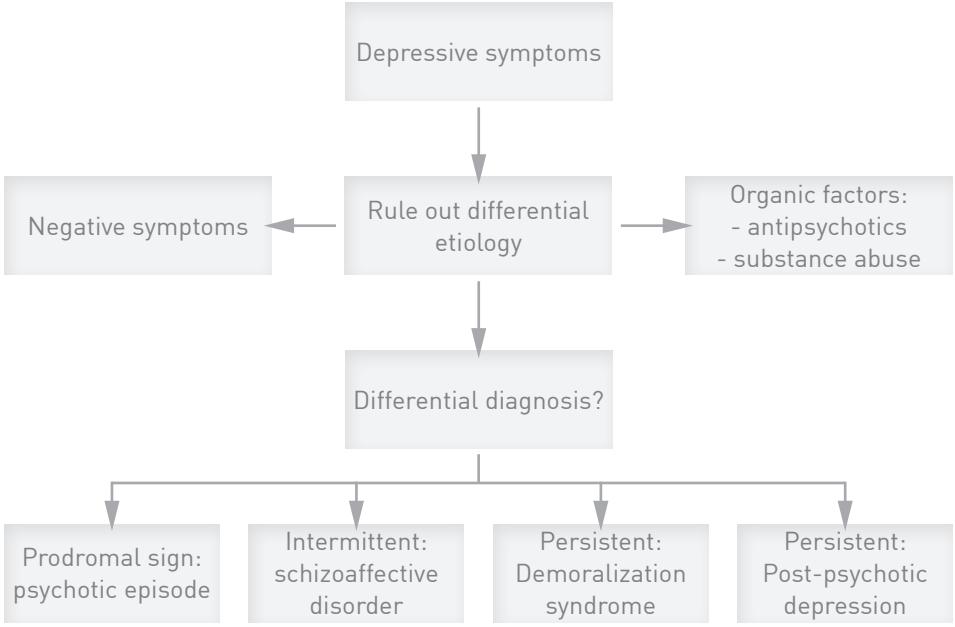
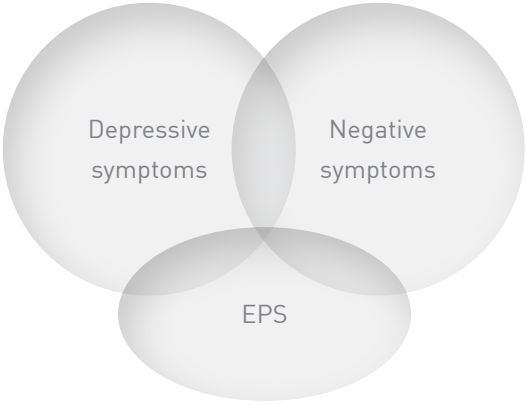


FIGURE 2. Patients with schizophrenia and depressive symptoms may suffer from negative and/or extrapyramidal symptoms (EPS) at the same time.



CASE MR. B Mr. B. is a 25 year old economy student, living independently. He has a blue mood since he was 12, though he was able to enjoy life. He has always been very shy, having few social contacts and feeling estranged from other people. Three years ago he started to hear voices. He received outpatient care for these voices, but also for his blue mood, mood swings, self-depreciation and social isolation. After temporary admission for treatment of acute psychosis, he is diagnosed with 295.30 Schizophrenia, paranoid type. His medication (olanzapine) suppressed the voices in a way that they no longer dominate the clinical picture.

At the moment he cannot focus on his study due to the "chaos in his mind". He attributes these concentration problems to his medication. Although he desires to have more social contact, his psychosis made him feel even more suspicious towards other people. He is not very confident in the future, but would like to give life another try. His depressive symptoms continue to be prominent and distressing, although he has the idea that they pass into emotional flattening.

The clinician investigated whether the emotional symptoms reflect negative symptoms or depressive symptoms as part of a differential diagnosis of schizoaffective disorder, dysthymia or post-psychotic depression. The score of Mr. B on the MADRS depression rating scale was 9 on a scale from zero to 60 and his CDSS depression score was 3 out of 27. Neither one of these scores was indicative for a depressive episode. PANSS rating for negative symptoms was 12 out of 49 with particularly high scores on social and emotional withdrawal. The outcomes on the rating scales indicated that negative symptoms were present more than depressive symptoms.

Based on the outcome of the rating scales, the clinician decided not to diagnose Mr. B. with depression. The symptoms were indicative for a developmental disorder, which needed additional investigation of his personal history. The clinician considered switching to clozapine in the presence of persistent positive symptoms. He referred the patient to psychosocial therapy to ameliorate the negative symptoms.

MONITORING DEPRESSIVE SYMPTOMS

MONITORING DEPRESSIVE SYMPTOMS Widely used guidelines recommend a careful differential diagnosis of depression in patients with schizophrenia, considering factors such as medication side effects.[28-30] These guidelines, however, do not advise any selective depression instrument to help the clinician to adequately distinguish depressive symptoms from other psychotic symptoms in clinical practice. Adequate recognition of depressive symptoms, as well as regular monitoring of symptomatic changes is essential to guide appropriate treatment in patients with schizophrenia.[31,32]

Many depression instruments are available to measure depressive symptoms, but they vary in reliability and validity in patients with schizophrenia. Most depression instruments primarily developed for use among depressed patients do not appear to selectively discriminate depressive symptoms from other symptom dimensions in schizophrenia.[33,34] Perhaps, for pragmatic reasons some of those instruments are still used in clinical practice.[35] A comparison of the psychometric properties of available depression instruments in patients with schizophrenia will aid clinicians and researchers to select a valid instrument for the measurement of depressive symptoms. Feasibility is another important consideration for selecting a depression instrument for the use in routine outcome monitoring.[36] Self-report is as good as interview-based assessment in the monitoring of change in psychopathology,[37] and preferred in routine clinical practice to save time and costs.[35] Furthermore, systematic use of patient-reported outcomes for the monitoring of depressive symptoms has shown to facilitate decision making in routine clinical care of patients with depression.[38]

wo self-report instruments that can be used for the measurement of depressive symptoms in schizophrenia received relatively little attention in the international literature. The Quick Inventory of Depressive Symptoms (QIDS-SR_{16}) has good psychometric properties in patients with depressive disorders and is sensitive to symptomatic changes.[39,40] The presence of psychotic symptoms did not meaningfully affect the propensity of self-rating to recognize depressive symptoms in patients with major depressive disorder.[41] The CES-D is an easy-to-use depression instrument, developed to monitor sub-syndromal depressive symptoms in the general population. The CES-D discriminates depressive symptoms from negative symptoms,[42] and the predictive validity of the CES-D has been shown to be sufficient to detect cases of depression in a population of mixed psychiatric disorders.[43] Nevertheless, the

performance of the latter instruments has not extensively been investigated in a population of patients with schizophrenia.

MONITORING DEPRESSIVE SYMPTOMS IN RESPONSE TO ANTIPSYCHOTICS

Patients frequently attribute depressive symptoms to the use of antipsychotics.[44-46] It is important to monitor these attributions to antipsychotics as part of disease management to prevent medication non-adherence.[47,48] Patients with schizophrenia have shown to rate their experiences with antipsychotics in a reliable way, possibly more accurate than clinician ratings.[49] This was confirmed by a significant correlation between patient reports of subjective experiences and their levels of dopamine D_2 receptor occupancy by antipsychotic drugs.[50] Furthermore, an interview may induce bias by responses that could be viewed favorably by others, whereas self-report is more neutral in this aspect. Two self-report instruments designed to assess subjective experiences in response to antipsychotics include depressive symptoms. The patients' attribution of depressive symptoms to antipsychotics can be monitored using the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS),[51] or the Subjects' Response to Antipsychotics (SRA) self-report scale.[52] The SRA is constructed of lay term expressions, based on original patient statements which may be easier understood than some of the clinical terms in the LUNSERS.[53] However, our own experience with the SRA-74 suggests that especially patients with concentration difficulties find it a long questionnaire with many questions addressing the same clinical effect. Reducing the total number of items with in the range of other scales (about 30 items)[51,53] would increase its feasibility for screening purposes.

TREATMENT OF DEPRESSIVE SYMPTOMS

TREATMENT GUIDELINES

Antidepressants may be added as an adjunct to antipsychotics when the depressive symptoms meet the syndromal criteria for major depressive disorder or cause significant distress.[28-30] But there is conflicting evidence on the effectiveness of antidepressants in the treatment of depressive symptoms in this population.[54,55] Caution is warranted, since adding antidepressants to antipsychotics may increase the risk of interactions and side effects and lead to higher medical costs.[29,56]

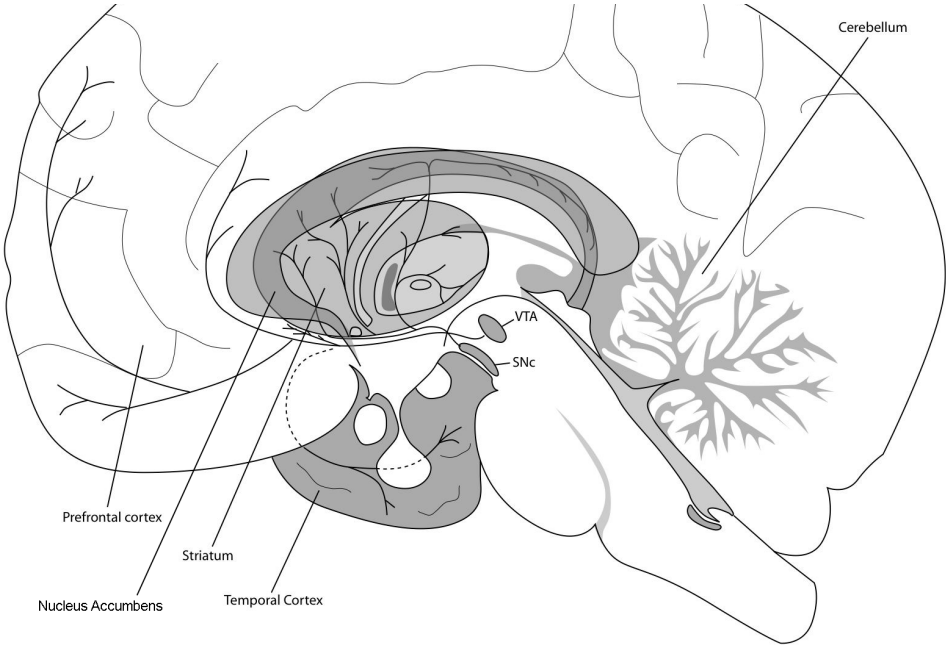
The most common distinction between antipsychotics is between the typical (first generation) antipsychotics (e.g. haloperidol, zuclopenthixol) and the newer atypical (second generation) antipsychotics (e.g. clozapine, risperidone, olanzapine), although there is still no universal consensus about the meaning of the term "atypical" besides a minimal risk of extrapyramidal side effects.[57] The American and Dutch guidelines prefer second generation antipsychotics over first generation antipsychotics in the treatment of patients with schizophrenia and co-morbid depressive symptoms,[29,30] although the evidence for this recommendation is poor.[58] The guidelines provide no specific recommendation to treat or prevent depressive symptoms in response to antipsychotics.[28-30]

DEPRESSIVE SYMPTOMS IN RESPONSE TO ANTIPSYCHOTICS Antipsychotic treatment is thought to relief psychotic symptoms by making abnormal perceptions or delusional beliefs less meaningful and intense. Antipsychotics reduce the overactive dopaminergic transmission by blockade of dopamine receptors in striatal brain areas.[59] Blockade of dopamine D_2 receptors in non-striatal brain regions (Figure 3) may, however, block emotional experiences.[60,61]

Early observations of antipsychotic-induced depressive symptoms associated these depressive symptoms with parkinsonian effects of dopaminergic blockade in the nigrostriatal pathways.[25,62] Nowadays patients using the second generation antipsychotics with a lower risk of these extrapyramidal side effects, still attribute depressive symptoms to antipsychotics.[44-46] Animal research showed how dopamine D_2 receptor blockade may disturb the reward system in other brain regions.[63,64] The resultant experience of relative anhedonia may resemble a depressed state.[6] Antipsychotics may affect brain regions involved in the pleasure of reward by blockade of the dopaminergic pathways projecting to the nucleus accumbens and prefrontal cortex.[65-68] Given that the dopamine transmission in the prefrontal cortex is already under-active in patients with schizophrenia,[69,70] additional dopaminergic blockade in this brain region could exacerbate emotional indifference.[71,72] Furthermore, antipsychotic affinity for the serotonin 5-HT_{2a} receptor has been proposed to mediate a reduction of depressive symptoms by modulating the dopaminergic system in these brain areas.[61] Thus antipsychotic-induced depressive symptoms may be mediated by different pharmacological mechanisms.

Epidemiological studies provided clinical evidence for antipsychotic-induced depressive symptoms by finding a dose-dependent effect of first generation antipsychotics.[73,74] Imaging studies found a similar association between altered emotional experiences and increased levels of D_2 receptor occupancy.[50,75-78] Altogether, antipsychotic D_2 receptor blockade is likely to be involved in the induction of depressive symptoms.

FIGURE 3. Brain areas containing the most dopamine receptors are striatal areas and dopaminergic pathways projecting from the ventral tegmental area (VTA) and substantia nigra compacta (SNc) to the nucleus accumbens, temporal cortex, prefrontal cortex and cerebellum; adapted from Loonen and Hovens, 2012.[79]



ANTIPSYCHOTICS DIFFER IN D_2 RECEPTOR AFFINITY AND OCCUPANCY

Antipsychotics differ in their binding affinity for the D_2 receptor,[57,80] which has implications for their therapeutic action and (emotional) side effects. The binding affinity constant (K_d) reflects the concentration of antipsychotic required to occupy 50% of the receptors at the equilibrium state in a test tube. In the human brain, however, the dynamic neurotransmission system does not allow these drug-receptor interactions to reach equilibrium. The binding affinity of an antipsychotic to the receptor can better be described by continuous association with the receptor (k_{on}) and

dissociation (k_{off}) from the receptor, as follows:

$$K_d[nM] = \frac{k_{on}}{k_{off}}$$

Differences in binding affinity of antipsychotics are driven by how fast they dissociate from the D_2 receptor (k_{off}),[80,81] whereas the association with the D_2 receptor (k_{on}) is considered equal between antipsychotics.[57] The review by Kapur elegantly describes how the occupancy of dopamine D_2 receptor in the brain depends on the dissociation (k_{off}) of the drug and the competition of the antipsychotic with endogenous dopamine.[57]

The faster the antipsychotic dissociates from the D_2 receptor (i.e. the lower the affinity for the D_2 receptor), the more quickly the drug can be displaced by dopamine as soon as the dopamine concentration rises. Antipsychotics with weak D_2 receptor affinity (quetiapine and clozapine) enable a quick response to instant changes in endogenous dopamine levels of the patient, for example an emotional response to a video game within seconds to minutes.[82] In contrast, the emotional system responds slower to such sudden dopamine surges in patients using antipsychotics with high affinity for the D_2 receptor, which dissociate more slowly from the receptor.[57]

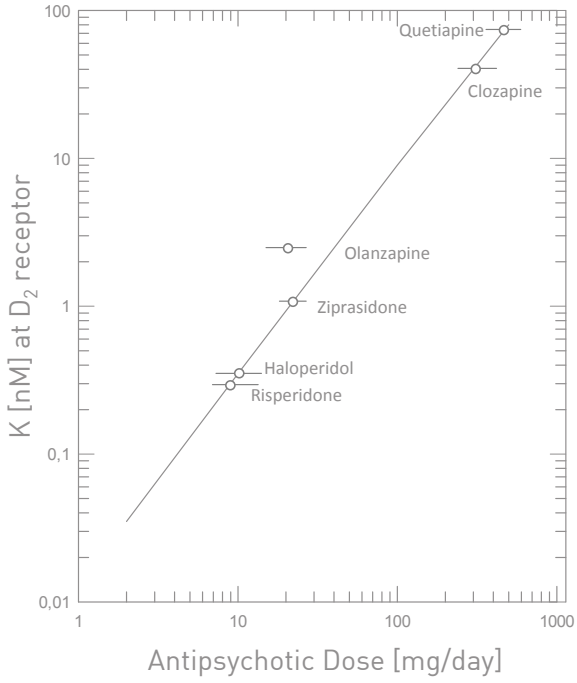
Also over timeframes of hours and days, the dissociation rate of antipsychotics may play a role in emotional experiences. Imaging studies have shown that administration of antipsychotics with weak affinity for the D_2 receptor give a transient peak level of about 60% D_2 receptor occupancy in the brain,[83] dropping quickly to 30%.[83,84] Antipsychotics with a high binding affinity for the dopamine D_2 receptor are likely to produce prolonged and high (60-80%) occupancy of D_2 receptors.[85] This continuous D_2 receptor occupancy may reduce the sensitivity to dopamine blockade at system level due to tolerance and receptor up-regulation,[86] which gives rise to extrapyramidal side effects and altered emotional experiences.[50,77] Theoretically, the risk of altered emotional experiences like depression would be reduced for antipsychotics with weak affinity for the D_2 receptor[61]

The relationship between antipsychotics and depressive symptoms may depend on antipsychotic D_2 receptors affinity and its occupancy of D_2 receptors in the brain. Generally, antipsychotics that dissociate faster from the D_2 receptor than endogenous dopamine are prescribed in relatively high doses (>100mg) (Figure 4). But high doses of these antipsychotics with weak D_2 receptor affinity are less likely to induce

D_2 receptor mediated emotional experiences than high doses of antipsychotics with a high D_2 receptor affinity.[87] So far, this hypothesis has been tested in studies with small study groups, minimal effect sizes and no control group using antipsychotics with weak affinity for the D_2 receptor.[75,77,78]

There is rising interest in meta-analysis of published imaging data, which can be used to develop dose-occupancy equivalents that estimate the level of D_2 receptor occupancy for a given antipsychotic dose. Lataster was the first to develop dose-occupancy equivalents that predict the mean level of occupancy of a population based on antipsychotic dose.[78] The dose-occupancy relationship has been described for antipsychotics with medium to high affinity for the D_2 receptor but not for weak dopamine antagonists like quetiapine.[78] Furthermore, previous meta-analyses did not take into account possible bias introduced by methodological differences between imaging studies.[88,89] The three-dimensional image of D_2 receptor occupancy in the brain may depend on the imaging technique (Positron Emission Tomography or Single Photon Emission Tomography) or the choice of radioligand that binds to the D_2 receptor.[90] The effect of methodological heterogeneity on the relation between antipsychotic dose and D_2 receptor occupancy is increasingly relevant in view of the raising interest in clinical implications of D_2 receptor occupancy data.[78,88,91-94] Dose-occupancy equivalents can be used to compare D_2 receptor mediated (side) effects between antipsychotics and doses in epidemiological and clinical studies. Finding a therapeutic dose window with minimal risk of side effects for antipsychotics may improve treatment strategies.[87,92,95]

FIGURE 4. The clinical antipsychotic doses needed for effective reduction of psychotic symptoms are correlated to the antipsychotic affinity for the D_2 receptor, represented by the dissociation constant K [nM]. Antipsychotics with a dissociation constant of K › 1.5 nM bind more loosely to the D_2 receptor than endogenous dopamine, adapted from Seeman and Tallerico (1998).[86]



RESEARCH AIMS AND OUTLINE OF THE THESIS

Goals in the clinical treatment of patients with schizophrenia and depressive symptoms are adequate screening and monitoring of depressive symptoms. Recognition of depressive symptoms is important to guide appropriate treatment of patients with schizophrenia and thereby improve their quality of life. The differential etiology (causes) and phenomenological overlap of depressive symptoms complicate the recognition of depressive symptoms in clinical practice clinicians. The first aim of this thesis is to optimize the screening and monitoring of depressive symptoms in clinical practice. We will focus on the patients' perspective by means of self-report. The second aim of this thesis is to describe the relationship between depressive symptoms and D_2 receptor affinity and occupancy.

Gaps of knowledge in literature on this topic are an overview of (self-report) depression instruments that are reliable and valid to use in patients with schizophrenia. It is also unclear whether depressive symptoms in response to antipsychotics represent a separate symptom dimension from other affective side effects. Furthermore, there is a lack of dose-occupancy equivalents describing antipsychotics with weak affinity for the D_2 receptor. Finally, the relation between depressive symptoms and antipsychotic D_2 receptor affinity and occupancy needs additional investigation for a wide range of antipsychotics, including antipsychotics with weak affinity for the D_2 receptor. We addressed these issues in the following Chapters:

Chapter 2 describes the course of depressive symptoms over time in relation to the prescription of antidepressants in clinical practice of patients with schizophrenia. Chapter 2 also describes predictors for the incidence and the persistence of depressive symptoms in patients with schizophrenia.

Chapter 3 provides an overview of depression instruments that can be used for the monitoring of depressive symptoms in patients with schizophrenia. Depression instruments are compared on their psychometric properties, including the ability to discriminate depressive symptoms from negative psychotic symptoms. Chapters 4 and 5 compare the validity of two self-report depression instruments with interview-based assessments of depressive symptoms in patients with schizophrenia.

Chapters 6 to 8 address the relationship between antipsychotics and depressive symptoms. Chapter 6 investigates whether patients attribute depressive symptoms to their antipsychotics independent from other experiences like drug-induced EPS and emotional flattening. In the same Chapter we develop a shorter version of a questionnaire to measure depressive symptoms and other experiences in response to antipsychotics. Chapter 7 describes the relationship between antipsychotic dose and dopamine D_2 receptor occupancy for eight frequently prescribed antipsychotics with distinct D_2 receptor affinities. We investigate the effects of methodological heterogeneity between studies on the variability of the estimated D_2 receptor occupancy across studies. The resultant dose-occupancy equivalents are implemented in Chapter 8, to investigate the involvement of D_2 receptor affinity and occupancy in patients attributing depressive symptoms to their antipsychotics.

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2

The course of depressive symptoms and prescribing patterns of antidepressants in schizophrenia in a one year follow-up study

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BACKGROUND Antidepressants are frequently prescribed in patients with psychotic disorders, but little is known about their effects in routine clinical practice. The objective was to investigate the prescribing patterns of antidepressants in relation to the course of depressive symptoms in patients with psychotic disorders.

METHODS A cohort of 214 Dutch patients with psychotic disorders received two assessments of somatic and psychiatric health, including a clinician-rated screening for depressive symptoms, as part of annual routine outcome monitoring.

RESULTS Depressive symptoms were prevalent among 43% (93) of the patients. Antidepressants were prescribed for 40% (86) of the patients and the majority 83% (71) continued this therapy after one year. Multivariable analysis showed that patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year (OR [95% CI] = 0.953 [0.912–0.995]). For patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms (OR [95% CI] = 1.593 [1.123–2.261]). Antidepressant use was not an independent predictor in both analyses.

CONCLUSIONS Routine outcome monitoring in patients with psychotic disorders revealed a high prevalence of depressive symptoms. Antidepressants were frequently prescribed and continued in routine clinical practice.

Depressive symptoms occur in about 25% of patients with schizophrenia,[1,2] but the reported prevalence may vary between 7% and 75%.[3-6] The variation is due to heterogeneous study populations, differences in study methods and differences in diagnostic criteria. Depressive symptoms may be present throughout all phases of schizophrenia.[6,7] The highest prevalence is found during acute psychotic episodes[8]. Persistent depressive symptoms during the chronic phase of illness have been associated with a higher risk for relapses.[9,10] Depressive symptoms may reflect a psychological reaction to the severe illness or 'demoralization syndrome',[11] or can partly mimic extrapyramidal side effects related to the dopamine blockade of antipsychotics, known as 'akinetic depression' or dysphoria.[5,12,13] Antipsychotic-induced depressive symptoms may be treated by lowering the antipsychotic dose, switching to another (atypical) antipsychotic or adding anticholinergic medication.[2,14] Guidelines for the treatment of schizophrenia advise prescribing antidepressants for depressive symptoms,[15-17] although there is conflicting evidence on the efficacy of antidepressants for depressive symptoms in schizophrenia from randomized controlled clinical trials.[18,19] Antidepressants are prescribed for 11 to 43% of the patients with schizophrenia.[20-22] They are commonly used to treat depressive symptoms, but may also be used for anxiety disorders or negative symptoms.[23-25] Adding antidepressants to antipsychotics increases the risk of interaction and side effects,[26] and may also lead to higher medical costs.

Longitudinal observational studies describing predictors for the development or persistence of depressive symptoms in patients with schizophrenia are scarce. Moreover, longitudinal studies describing the course of depressive symptoms do not report details of prescribing patterns of antidepressant therapy.[10,27-29] It is unclear how many patients with persistent depressive symptoms continue to use antidepressants or remain untreated with antidepressants. The current naturalistic study is based on a cohort of patients with schizophrenia or related psychotic disorders, assessed during yearly routine outcome measurements. The aim is to investigate the course of depressive symptoms in relation to prescribing patterns of antidepressants in schizophrenia during one year follow-up.

All patients of 18 years and older with schizophrenia or related psychotic disorders covered by a mental health care centre in a circumscribed area in the Netherlands were included in yearly routine outcome assessments of their physical and mental health as described previously.[30,31] Assessments were carried out between January 2003 and April 2006 in patients having given informed consent in accordance with the latest version of the Declaration of Helsinki. Patients were included if they completed a first (baseline) and second assessment (follow-up) within an interval of 12 months (±3 months). In-patients with an acute psychosis at first assessment were excluded from analysis. Trained nurses conducted a structured interview lasting approximately one hour to evaluate the patients' social functioning, mental and physical health status. Current medication use was retrieved from the patient's medical records and was than confirmed with the patient. A psychiatrist based the diagnosis on the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) classification system (codes 295.4 - 295.9, 297.1, 298.8 and 298.9).[32] The patient's psychiatrist rated depressive and extrapyramidal symptoms on a 3-point Likert scale (absent, moderate, severe) and assessed psychosocial functioning using the Global Assessment of Functioning scales (GAF-Symptoms and GAF-Disability).

Patients with moderate or severe depressive symptoms were categorized as 'having depressive symptoms'. Baseline characteristics were compared a) between patients who did not have depressive symptoms at both assessments and patients who developed depressive symptoms at second assessment ('incidence'); b) between patients with depressive symptoms at baseline that were no longer present at second assessment ('remitted') and patients with depressive symptoms present at both assessments ('persistent').

We analyzed potential predictors of depressive symptoms at follow-up. As a first step we compared baseline characteristics between patients with and without depressive symptoms at follow-up in a univariable analysis. Categorical variables were tested using a chi-square test and continuous variables were not normally distributed and were therefore assessed by the non-parametric Mann-Whitney U test. Multivariable logistic regression analysis was used to identify baseline patient characteristics as independent predictors of the incidence or the persistence of depressive symptoms at follow-up. Only those baseline characteristics with a significance level of $p<0.25$ in the univariable analysis were entered as predictors in the model. Significance levels greater than 0.05 are commonly applied to select predictors for multivariable

analysis.[33] In the multivariable analysis, a probability level of $p<0.05$ was accepted as statistically significant. All p-values are two-sided. In a more detailed description of the prescribing patterns of antidepressants, the course of depressive symptoms was compared between patients not using antidepressants at both assessments and patients who used antidepressants at both assessments by calculating the confidence intervals for these groups.

A total of 473 patients were eligible for inclusion into the study. Of those, 34% (162) did not want to participate in a second assessment or were lost to follow-up, e.g. moved away. 21% (97) patients had their second assessment not within 9 to 15 months. The remaining 45% (214) patients with a period of 11.8 (SD 1.7) months between first and second assessment were included in the study. The mean age was 38.7 years (SD 11.7; range 16-65 years) and mean duration of illness was 12.2 years (SD 9.4; range 1-44 years); 43% (92) were female, 76% (162) suffered from schizophrenia and the majority was outpatient (Table 1). Patients included in the study did not differ from the 259 not-included patients regarding age, duration of illness and prevalence of depressive symptoms at baseline. The proportion of females and outpatients was somewhat higher in the group of included patients, as was the proportion of patients using antidepressants and the average GAF-scores. Depressive symptoms were present among 43% (93) of the patients included and antidepressants were prescribed for 40% (86) patients, of whom 83% (71) continued their antidepressant therapy.

TABLE 1. A comparison of relevant variables of the total population at baseline (N=473).

	Study sample (N=214)	Not included (N=259)	Chi-Square or Z-value		P-value
Gender, female (%; N)	43% (92)	34% (88)	x^2 =	4.04	0.044
Age (mean; SD)	38.7 (11.7)	39.6 (12.6)	Z =	-1.14	0.255
Duration of illness (mean; SD)	12.2 (9.4)	11.1 (9.8)	Z =	-1.25	0.211
Diagnosis (%; N)			x^2 =	1.02	0.602
Schizophrenia	76% (162)	78% (201)			
Schizoaffective	20% (43)	17% (44)			
Psychotic disorder NOS	4% (9)	5% (14)			
Treatment status (%; N)			x^2 =	7.34	0.026
Outpatients	64% (138)	64% (167)			
Sheltered housing facilities	21% (44)	13% (34)			
Chronic inpatients	15% (32)	22% (58)			
Symptomatology (mean; SD)					
GAF-Symptoms	65.6 (15.1)	59.0 (18.5)	Z =	-5.02	0.000
GAF-Disability	61.0 (16.0)	56.4 (16.4)	Z =	-4.22	0.000
Depressive symptoms (%; N)	43% (93)	37% (97)	x^2 =	1.76	0.185
Antidepressants (%; N)	40% (86)	27% (69)	x^2 =	8.89	0.003

N=number; SD=standard deviation; NOS= Not Otherwise Specified; GAF=Global Assessment of Functioning. Categorical variables were analyzed by a two-sided chi-square test and continuous variables by a Mann-Whitney U test.

TABLE 2. Baseline characteristics of patients with and without depressive symptoms at follow-up (N=214).

	No depressive symptoms (N=136)	Depressive symptoms (N=78)	Chi-Square or Z-value		P-value
Gender, female (%; N)	46% (62)	38% (30)	x^2 =	1.03	0.311
Age (mean; SD)	38.4 (12.2)	39.4 (11.0)	Z =	-0.69	0.489
Duration of illness (mean; SD)	11.6 (9.6)	13.3 (8.9)	Z =	-1.63	0.103
Diagnosis (%; N)			x^2 =	3.04	0.219
Schizophrenia	76% (103)	76% (59)			
Schizoaffective	18% (25)	23% (18)			
Psychotic disorder NOS	6% (8)	1% (1)			
Treatment status (%; N)			x^2 =	0.56	0.756
Outpatients	66% (90)	62% (48)			
Living in sheltered housing facilities	19% (26)	23% (18)			
Chronic inpatients	15% (20)	15% (12)			
Psychosocial status (%; N)					
No daytime activities	29% (36)	24% (18)	x^2 =	0.58	0.447
No contact with friends	31% (42)	21% (16)	x^2 =	2.70	0.100
No contact with family	12% (16)	6% (5)	x^2 =	1.61	0.205
Symptomatology (mean; SD)					
GAF-Symptoms	66.9 (15.9)	63.4 (13.2)	Z =	-1.58	0.113
GAF-Disability	61.3 (16.9)	60.4 (14.3)	Z =	-0.75	0.454
Extrapyramidal symptoms (%; N)	15% (20)	18% (14)	x^2 =	0.39	0.532
Depressive symptoms	29% (40)	68% (53)	x^2 =	29.96	0.000
Antipsychotics (%; N)			x^2 =	3.29	0.349
Atypical antipsychotics	69% (94)	62% (48)			
Typical antipsychotics	10% (14)	13% (10)			
Combination atypical + typical	10% (14)	18% (14)			
No antipsychotics	10% (14)	8% (6)			
Number of drugs prescribed (mean; SD)	2.4 (1.6)	3.3 (2.3)	Z =	-2.81	0.005
Number of drugs prescribed; excl.antidepr.	2.0 (1.4)	2.8 (2.2)	Z =	-2.41	0.016
Antidepressants (%; N)	35% (47)	50% (39)	x^2 =	4.92	0.027
Anticholinergics	4% (5)	9% (7)	x^2 =	2.63	0.105
Benzodiazepines	32% (43)	40% (31)	x^2 =	1.45	0.229
Moodstabilizers	13% (17)	14% (11)	x^2 =	0.11	0.738
Type of antidepressant (%; N)			x^2 =	1.10	0.576
Selective serotonin reuptake inhibitors	60% (28)	62% (24)			
Tricyclic antidepressants	17% (8)	23% (9)			
Other antidepressants	23% (11)	15% (6)			

N=number; SD=standard deviation; NOS= Not Otherwise Specified; GAF=Global Assessment of Functioning; excl.antidepr = exclusive antidepressants; anticholinergics included biperiden, dexetimide and trihexyphenidyl. Categorical variables were analyzed by a two-sided chi-square test and continuous variables by a Mann-Whitney U test.

Univariable analysis showed that depressive symptoms at follow-up were potentially associated with the following baseline characteristics with a p-value ‹ 0.25: duration of illness, diagnosis, no contact with friends or family, GAF-symptoms, depressive symptoms at baseline, antidepressant use, number of drugs other than antidepressants, use of benzodiazepines and anticholinergics (Table 2). These variables, except for use of benzodiazepines and anticholinergics being covered by the number of other drugs than antidepressants, were entered into a multivariable analysis to identify independent predictors of either the incidence or the persistence of depressive symptoms at follow-up.

Of the 121 patients without depressive symptoms at baseline, 79% (96) remained free of symptoms and 21% (25) patients newly developed depressive symptoms at second assessment (Table 3). Patients with a lower GAF-symptom score at baseline had a higher risk of developing depressive symptoms (N=121, Odds-Ratio [95% Confidence Intervals] = 0.953 [0.912-0.995], p‹0.030), when adjusting for the subset of clinical and socio-demographic characteristics as mentioned above. Of the 93 patients with depressive symptoms at baseline, 43% (40) 'remitted' (i.e. were free of depressive symptoms at second assessment) and 57% (53) had 'persistent' depressive symptoms after one year. Prescription of a higher number of drugs at baseline was a risk factor to have persistent depressive symptoms at follow-up (N=93, OR [CI] = 1.593 [1.123-2.261], p‹0.009).

The course of depressive symptoms in relation to antidepressant therapy is illustrated in Table 3. Of the patients without depressive symptoms at first assessment, 35% (42/121) were prescribed antidepressants; of whom 34 continued antidepressant therapy. Of these 34 patients 26% (9/34; CI: 12-49%) developed symptoms despite antidepressant therapy (incidence). The remaining patients without depressive symptoms at first assessment 65% (79) were prescribed no antidepressants; 70 of them did not start antidepressants between first and second assessment. The incidence rate in the latter group was 16% (11/70; CI: 7-30%). Of the patients with depressive symptoms at first assessment, 47% (44/93) were prescribed antidepressants; 37 of them continued their antidepressants at follow-up. 70% (26/37; CI: 56-85%) of them had persisting depressive symptoms despite continuing antidepressants, of whom only 4 switched type of antidepressants at second assessment. Of the patients with depressive symptoms at first assessment, 53% (49) did not use antidepressants and 41 of them did not start antidepressants between first and second assessment. The percentage of patients with persistent depressive symptoms was 49% (20/41; CI: 33-64%).

TABLE 3. Course of depressive symptoms and antidepressant therapy between baseline and follow-up (N=214).

Baseline	N	Follow-up	N	Antidepressant prescription	N
No depressive symptoms					
antidepressants	42	no depressive symptoms	32	discontinued	7
		incidence of depressive symptoms	10	discontinued	1
no antidepressants	79	no depressive symptoms	64	started	5
		incidence of depressive symptoms	15	started	4
Depressive symptoms					
antidepressants	44	remitted from depressive symptoms	15	discontinued	4
		persistent depressive symptoms	29	discontinued	3
no antidepressants	49	remitted from depressive symptoms	25	started	4
		persistent depressive symptoms	24	started	4

N=number; Changes in antidepressant prescription between baseline and follow-up were indicated by 'discontinued' (patients who used antidepressants at 1st assessment, but discontinued their therapy before the 2nd assessment) or 'started' (patients who did not use antidepressants at 1st assessment, but started before the 2nd assessment).

This naturalistic study showed a high prevalence rate (43%) of depressive symptoms in patients with psychotic disorders. Although the modal prevalence rate reported in the meta-analysis by Siris and Bench was 25%,[2] the findings were in line with comparable studies.[22,28] Previous cross-sectional studies have shown that depressive symptoms are associated with more severe psychopathology and (related) polypharmacy.[9,28,34-37] Our longitudinal study showed that these patient characteristics are also predictors of depressive symptoms. Patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year. For patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms. Also in accordance with previous studies, depressive symptoms were not associated with age, gender, duration of illness or being institutionalized.[7,28,36,38-41] Antidepressant use at baseline was related to the presence of depressive symptoms at follow-up in univariable analysis. However multivariable analysis indicated that antidepressant use was neither an independent predictor of remaining symptom free, nor of remitting from depressive symptoms.

Antidepressants were frequently prescribed in routine clinical practice as in previous studies.[3,28,36,42] Our study brought new insight into the prescribing patterns of antidepressants in relation to the course of depressive symptoms. The majority of antidepressants were continued once prescribed. A large proportion of patients appeared to have persistent depressive symptoms despite continuation of antidepressant treatment. Patients' symptoms may have remitted and reoccurred at second assessment or they may be non-responders. Another group continued antidepressants even though they remained free of depressive symptoms both years. Their antidepressant therapy may have served as an effective prophylaxis,[43,44] for other indications such as negative symptoms or anxiety or it may indicate overprescribing. In contrast, a considerable proportion of patients did not receive antidepressants despite experiencing persistent depressive symptoms which may suggest underprescribing.

The prescribing patterns may reflect the state of guidelines for schizophrenia. Current schizophrenia guidelines recommend to use antidepressants in patients with depressive symptoms, but do not give detailed prescribing advice, in particular about discontinuation in non-responders and duration of maintenance therapy.[16,17] Some guidelines refer for prescription of antidepressants to the depression guideline,[15] although it is doubtful whether depressive symptoms in schizophrenia should be treated the same way as major depressive disorder. One of the reasons for the lack of detail in the guidelines is

the scarcity of evidence about effectiveness of antidepressants in schizophrenia,[18,19] but also for depression in general.[45] More placebo-controlled research into the effectiveness of antidepressants is needed for the development and improvement of guidelines for prescription of antidepressants in schizophrenia.

Our study has the following limitations. Firstly, we cannot make firm conclusions regarding the effectiveness of antidepressants given the limitations of the naturalistic approach of the current study. This approach may give rise to 'confounding by indication' as in all observational research, i.e. patients using antidepressants may be more severely ill and thus would be more likely to have recurrent or persistent depressive symptoms. This is (partly) corrected for in our logistic regression. Other possible confounders in the apparent lack of antidepressant effect could have been poor compliance, prescription of inadequate doses in patients with antidepressants, or non-pharmacological treatments such as psychotherapy in patients without antidepressants. Secondly, depressive symptoms were clinician-rated instead of by a depression instrument validated for schizophrenia. We therefore cannot be sure whether the clinicians adequately distinguished depressive symptoms from negative symptoms. Thirdly, long-term follow-up is considered difficult in patients with schizophrenia,[22,46] but we achieved a reasonable response rate of 45%. Our study-sample differed from the patients who were not included in male/female ratio and level of functioning. The higher proportion of females in our study sample may explain the higher number of outpatients and the higher GAF-scores, as well as the increased use of antidepressants.[36,42,47] Despite these differences, the comparison of our findings with earlier studies as discussed above suggest that our sample is overall representative of a population with schizophrenia and related psychotic disorders. Lastly, depressive symptoms are known for their waxing and waning over time.[28] We measured symptoms once a year as part of our routine outcome monitoring, but a shorter time frame may be needed to follow patients with depressive symptoms.

In conclusion, our findings indicate that depressive symptoms occur frequently in clinical practice patients. We also found high prescription rates of antidepressants, and most patients continued their antidepressant medication once prescribed. Patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year. For patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms. We therefore would recommend close monitoring of the treatment in patients with depressive symptoms, in particular those with predictors present.

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3

A systematic review of instruments to measure depressive symptoms in patients with schizophrenia

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BACKGROUND Depressive symptoms require accurate recognition and monitoring in clinical practice of patients with schizophrenia. Depression instruments developed for use in depressed patients may not discriminate depressive symptoms from negative psychotic symptoms. We reviewed depression instruments on their reliability and validity in patients with schizophrenia.

METHODS A systematic literature search was carried out in three electronic databases. Psychometric properties were extracted for those instruments of which reliability, divergent, concurrent and predictive validity were reported in one or more publications.

RESULTS Forty-eight publications described the reliability and validity of six depression instruments in patients with schizophrenia. The only self-report was the Beck Depression Inventory (BDI). The Brief Psychiatric Rating Scale-Depression subscale (BPRS-D), Positive And Negative Syndrome Scale-Depression subscale (PANSS-D), Hamilton rating scale for Depression (HAMD), Montgomery Asberg Depression Rating Scale (MADRS) and Calgary Depression Scale for Schizophrenia (CDSS) were clinician rated. All instruments were reliable for the measurement of depressive symptoms in patients with schizophrenia. The CDSS most accurately differentiated depressive symptoms from other symptoms of schizophrenia (divergent validity), correlated well with other depression instruments (concurrent validity), and was least likely to miss cases of depression or misdiagnose depression (predictive validity).

CONCLUSIONS We would recommend to use the CDSS for the measurement of depressive symptoms in research and in daily clinical practice of patients with schizophrenia. A valid self-report instrument is to be developed for the use in clinical practice.

Depressive symptoms are highly prevalent (25%) in patients with schizophrenia.[1,2] These comorbid depressive symptoms are associated with a higher burden of disease and more frequent relapses.[3-5] Schizophrenia is a lifelong psychiatric disorder and depressive symptoms may occur through all phases of illness: during acute psychosis,[6,7] as well as after remission of psychosis.[8] Recent literature suggests that depressive symptoms may also be understood as a dimension within the schizophrenia concept and that individual symptom profiles should guide treatment.[9] Furthermore, the upcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) advocates to measure psychopathology in terms of quantitative dimensions, instead of solely as discontinuous categories (http://www.dsm5.org). Adequate screening and monitoring of depressive symptoms is required to guide appropriate treatment.[10-12].

Measurement instruments can be helpful for screening and for monitoring of symptomatic changes.[13] The assessment of depressive symptoms is complicated in patients with psychotic disorders, as they resemble 'classic' symptoms of schizophrenia, such as negative symptoms and extrapyramidal symptoms (EPS).[1,14-16] Particularly drug-induced parkinsonism may resemble a depressed state.[17] It is doubtful whether instruments, primarily developed for use among depressed patients, are able to selectively discriminate depressive symptoms from other symptom dimensions in schizophrenia (divergent validity).[18,19] Currently there is no overview of available depression instruments and their psychometric properties in patients with schizophrenia.

This systematic review provides an overview of instruments that can be used for the screening on depressive symptoms (further referred to as 'depression instruments'). Instruments are compared regarding their divergent validity and other psychometric properties in this patient population. This review may help in choosing a suitable instrument for the measurement of depressive symptoms in research as well as in daily clinical practice of patients with schizophrenia.

SEARCH PROCEDURE As a first step, titles and abstracts were screened on relevance for the defined topic and, if appropriate, the full paper was examined. Inclusion criteria were: 1) studies assessing psychometric properties of instruments measuring depressive symptoms in a population of patients with schizophrenia or non-affective psychotic disorders, 2) the availability of a validated English translation of the depression instrument and 3) publication in English, German, French or Dutch language. Unidimensional depression instruments (measuring a single dimension, in this case depressive symptoms), as well as multidimensional instruments measuring multiple symptom dimensions providing a subscale for depressive symptoms, were included. We refer to the depression subscale of a multidimensional instrument by the addition of [-D] to the abbreviation of the instrument, for example BPRS-D. We excluded studies describing diagnostic instruments and instruments designed to measure related symptoms, such as anxiety or suicidality.

The following search terms were entered in the online databases PubMed, EMBASE and PSYCHINFO: ((“depression” or “depressive symptoms”) AND (“schizophrenia” OR “psychosis” OR “psychotic”) AND (“instrument” OR “rating scale” OR “scale” OR “questionnaire” OR “interview”) AND (“psychometric” OR “reliability” OR “validation” OR “validity” OR “reproducibility”)). The search was carried out in May 2010. All retrieved studies were checked for cross-references.

GENERAL INFORMATION General information about the most recent version of each instrument was collected from (original) validation studies and the Handbook of Psychiatric Measures.20 In order to quantify the recent use of the selected instruments in research, we counted the number of studies published between May 2005 and May 2010. The composition of each depression instrument was explored as follows. Each item of an instrument was categorized under one the nine diagnostic criteria for a Major Depressive Episode (MDE), defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).21 Remaining items were categorized under three additional symptom dimensions: “delusional ideas”, “other vital symptoms” and “anxiety”. Four of the nine diagnostic criteria for MDE show overlap with symptom dimensions of schizophrenia, in particular negative symptoms and extrapyramidal symptoms. For each instrument, the number of potentially overlapping items was divided by the total number of items. This illustrated the instruments’ ability to discriminate depressive symptoms from other symptom dimensions of schizophrenia.

Psychometric properties were extracted for those instruments of which reliability, divergent, concurrent and predictive validity were reported in one or more publications. In the next paragraphs we explain these psychometric properties.

RELIABILITY Reliability is generally estimated by internal consistency, inter-rater and test-retest reliability. Internal consistency reflects the coherence between items within an instrument. Corresponding Cronbach's alpha values of 0.60-0.70 are considered acceptable and values of › 0.70 as good.[22] Good inter-rater and test-retest reliability is reflected by little variation between the scores by different raters and, respectively, by repeated measurements; these are commonly expressed by Intra-Class Coefficients (ICC) › 0.70.

DIVERGENT VALIDITY Divergent (or discriminant) validity refers to the extent that different symptom dimensions are unrelated to each other. Here, an instrument designed to measure depressive symptoms, should not measure negative symptoms, EPS or anxiety as well. Divergent validity is commonly expressed by the Pearson's Product Moment Correlation (PPMC) between scores on a depression instrument and scores on an instrument measuring another symptom dimension. Absent correlation with negative symptoms or EPS indicates good divergent validity. Nevertheless weak correlations (‹0.30) are acceptable, as depressive symptoms tend to occur together with negative symptoms and EPS.[16,23]

Divergent validity can also be evaluated on the stability of the underlying factor structure of a particular instrument across different samples. For multidimensional instruments, Principal Component factor Analysis (PCA) should identify depressive symptoms as a separate factor from psychotic symptom dimensions. In addition, the content of this depression factor should remain stable by confirmatory factor analysis in different samples. PCA of unidimensional instruments in a population with schizophrenia should identify factors describing depressive symptom dimensions, but no psychotic symptom dimensions.

CONCURRENT VALIDITY Concurrent (or convergent) validity refers to the extent that common symptom dimensions are in fact related. Concurrent validity is high when the scores on two instruments measuring the same symptom dimension correlate well (PPMC). Based on the mean correlation of each possible comparison between two instruments, we calculated a pooled mean correlation over all comparisons for each instrument.

PREDICTIVE VALIDITY Predictive validity represents the accuracy of an instrument to correctly detect a case (here of depression). Included were publications using a validated diagnostic interview such as the Structured Clinical Interview for DSM-IV as gold standard to identify positive cases of depression.[24] Good predictive validity is reflected by high sensitivity (not likely to miss cases of depression) combined with high specificity (not likely to misdiagnose depression) at the optimal cut-off value, i.e. the best balance between sensitivity and specificity determined by area under the receiver operating curve methods.[25]

INCLUSION OF STUDIES The systematic search generated a total of 2642 articles, of which 57 publications were eligible for further evaluation (Figure 1).

For six depression instruments complete information on psychometric properties in a population with schizophrenia or psychotic disorders was described in 49 publications. These included two multidimensional instruments: the Brief Psychiatric Rating Scale, Expanded Version (BPRS),[26,27] and the Positive And Negative Syndrome Scale (PANSS),[28] and four unidimensional instruments: the Hamilton Rating Scale for Depression (HAMD),[29] Montgomery Asberg Depression Rating Scale (MADRS),[30] Calgary Depression Scale for Schizophrenia (CDSS),[31] and Beck Depression

FIGURE 1. Flow diagram of publications identified in databases PsychINFO, Medline and PubMed with keywords for schizophrenia, depressive symptoms and psychometrics.

Inventory-II (BDI).[32] The remaining 8 publications described depression instruments with incomplete information about their psychometric properties in schizophrenia. For example, no information was available on reliability or divergent validity in schizophrenia for the Brief Symptom Inventory (BSI),[33] and Center for Epidemiologic Studies Depression Scale (CES-D).[34]

GENERAL CHARACTERISTICS General characteristics of the six reviewed depression instruments are described in Table 1. Only one instrument was based on self-report. Unidimensional instruments required on average 10 minutes less time to be completed than multidimensional instruments. The number of items per depression instrument varied between 4 and 21. A quantitative investigation of the use of these depression instruments over the past five years showed that the CDSS was most frequently used in research in this period, closely followed by the PANSS-D and the HAMD.

TABLE 1. General characteristics of reviewed instruments.

	Symptom dimensions	Mode	Training	Duration (minutes)	Time-frame	Number of items	Likert scale	Recent use
BPRS	multidimensional	clin.r.	++	25-40	2 weeks	24	7	3
PANSS	multidimensional	clin.r.	+++	30-40	1 week	30	7	6
HAMD	unidimensional	clin.r.	+	20	3 days	17	5	5
MADRS	unidimensional	clin.r.	+	15	1 week	10	4	1
CDSS	unidimensional	clin.r.	++	15-20	2 weeks	9	4	6
BDI	unidimensional	self-r.	n.a.	10	2 weeks	21	4	4

BPRS = Brief Psychiatric Rating Scale; PANSS = Positive And Negative Syndrome Scale; HAMD = Hamilton rating scale for Depression; MADRS = Montgomery Asberg Depression Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; BDI = Beck Depression Inventory. clin.r. = clinician rated; self-r. = self-rated. The amount of training needed to standardize raters varied between + (reading the instructions and/or a single consensus training), ++ (a short training session, followed by ↗ 3 times of practice) and +++ (more than one day of training); n.a. = not applicable. Recent use was expressed by the number of publications reporting the use of an instrument for the measurement of depressive symptoms in patients with schizophrenia between 2005-2010.

Table 2 illustrates the composition of the depression instruments in the context of schizophrenia. The depressive symptoms covered by the CDSS had minimal overlap with other symptom dimensions of schizophrenia. In contrast, about three quarter of the items of the PANSS-D and BPRS-D showed overlap with anxiety and positive symptoms. The HAMD contained many items on delusional symptoms. Almost half of the items of the MADRS and BDI could also be interpreted as negative symptoms.

TABLE 2. Composition of instruments evaluating depressive symptoms in schizophrenia

Symptom dimensions	Symptoms	MDE criteria	BPRS -D	PANSS-D	HAMD	MADRS	CDSS	BDI
depressive symptoms	depressed mood [a]	1	1	1	1	3	4	4
	changed appetite or weight	1	-	-	2	1	-	1
	sleeping problems	1	-	-	3	1	1	1
	worthlessness [b]	1	-	-	-	-	2	4
	suicidal ideation	1	1	-	1	1	1	1
negative symptoms	loss of interest or pleasure	1	-	-	-	1	-	2
	fatigue / lack of initiative or motivation	1	-	-	1	1	-	2
	indecisiveness / lack of concentration	1	-	-	-	1	-	2
EPS	psychomotor agitation or retardation	1	-	-	2	-	-	1
other	delusional ideas [c]	-	3	2	3	-	1	2
	other vital symptoms [d]	-	-	-	2	-	-	1
	anxiety / tension [e]	-	1	2	2	1	-	-
Items identifying symptoms in non-depressive dimensions		4	4	4	10	4	1	10
Total number of items of the (sub)scale [f]		9	6	5	17	10	9	21
% of items identifying non-depressive dimensions		44%	67%	80%	59%	40%	11%	48%

Depressive symptoms (dimensions) potentially overlapping with psychotic symptoms. a) Appeared or perceived depressed mood, including hopelessness, crying, pessimism, irritability and diurnal variation of mood. b) Including self-blame and non-delusional feelings of guilt. c) Including paranoid symptoms, hypochondriacal delusions, feeling criticized by others, poor insight and delusional feelings of guilt or punishment. d) Including loss of libido and somatization, e) including obsessional and compulsory symptoms. f) Depression subscale of the BPRS as defined by Dingemans (1995);[35] depression subscale of the PANSS as defined by Kay (2000).[28]

RELIABILITY The internal consistency of the BPRS-D was acceptable and good for the remaining instruments in schizophrenia (Table 3a). The inter-rater and test-retest reliability was good for all instruments, especially the inter-rater reliability of the HAMD.

DIVERGENT VALIDITY The MADRS correlated with negative symptoms and the HAMD with EPS, whereas the other reviewed instruments neither showed substantial correlation with negative nor extrapyramidal symptom dimensions (Table 3b). The following instruments were used for the rating of negative and extrapyramidal symptoms: Affective Flattening Scale (AFS);[71] Scale for the Assessment of Negative Symptoms (SANS);[72] negative subscale of the PANSS;[28] negative subscale of the BPRS;[26,27] Psychomotor Retardation Scale,[73] and Rating Scale for Extrapyramidal Side Effects.[74]

The underlying factor structure of the multidimensional instruments (BPRS and PANSS) generally consisted of one factor for depression and two to four other factors. The depression factor was comprised of the three items "depression", "guilt" and "anxiety",[75,76] but additional items loading on the depression factor were "tension",[37,77-79] "somatic concern",[42,60,80,81] and "suicidality",[82,83] or other combinations including "self neglect",[35] or "motor retardation".[84] Inspection of the factor structure of the MADRS and the CDSS did not lead to separate factors for negative symptoms.[37,42,85] The BDI consisted of three factors, including one for "psychosomatic symptoms".[53] Of note, no publications reported the factor structure of the HAMD in patients with schizophrenia.

CONCURRENT VALIDITY The concurrent validity of the depression instruments in schizophrenia is described in Table 3c. Concurrent validity has been assessed for almost every possible combination of the six instruments. The HAMD was most frequently investigated (by 19 comparative studies), followed by the CDSS, PANSS-D, BDI, BPRS-D and MADRS. The highest concurrent validity indices were found for the CDSS and MADRS.

PREDICTIVE VALIDITY Four studies evaluated whether the six depression instruments adequately predicted the presence of MDE in patients with schizophrenia. Table 3d illustrates that the highest ranges for sensitivity and specificity were found for the CDSS. Of note, the optimal cut-off values obtained for the CDSS and PANSS-D varied widely between studies.

TABLE 3. Aspects of reliability and validity of depression instruments in schizophrenia

A. RELIABILITY

	Internal consistency	Inter-rater	Test-retest	References
BPRS-D	0.67	0.74	0.72	[31,36]
PANSS-D	0.77	0.80	-	[37,38]
HAMD	0.75 (0.73 - 0.77)	0.94 (0.93 - 0.95)	0.75 (0.65 - 0.80)	[31,36,39-41]
MADRS	0.91	0.81	0.71	[37,41,42]
CDSS	0.82 (0.76 - 0.88)	0.86 (0.73 - 0.98)	0.83 (0.69 - 0.93)	[31,39-41,43-52]
BDI	0.90 (0.88 - 0.91)	n.a.	-	[31,53]

B. DIVERGENT VALIDITY

	Negative symptoms	References	EPS	References
BPRS-D	0.00 (-0.11 – 0.10)	[36,54,55]	0.14 (0.07 - 0.21)	[56,57]
PANSS-D	0.19 (-0.11 – 0.41)	[19,37,49,55,58-60]	0.07 (0.01 - 0.20)	[19,56,58,59]
HAM-D	0.18 (0.02 – 0.45)	[36,49,55,57-64]	0.40 (0.02 - 0.79)	[48,56-59]
MADRS	0.36 (0.12 – 0.51)	[19,37,49,57]	0.52 (0.16 - 0.86)	[19,48,57]
CDSS	0.10 (-0.24 – 0.54)	[43,45-49,55,57-60,65,66]	0.26 (0.07 - 0.42)	[43,45,47,48,56-59,65,66]
BDI	0.10 (-0.11 – 0.21)	[53,59,64,67]	0.23	[59]

C. CONCURRENT VALIDITY

	BPRS-D	PANSS-D	HAMD	MADRS	CDSS	BDI	Pooled mean	References
BPRS-D		0.23	0.66	0.66	0.79	0.64	0.60 (0.17 - 0.87)	[31,36,39,55,57,61,68,69]
PANSS-D			0.62	0.72	0.66	0.49	0.54 (0.17 - 0.87)	[19,37,41,43,45,47,49,53,55,58-60,69]
HAMD				0.80	0.74	0.57	0.68 (0.26 - 0.90)	[31,36,39,41,42,45,47-49,55,57-61,63,64,67,70]
MADRS					0.81	-	0.75 (0.56 - 0.90)	[19,37,41,42,45,48,49,57]
CDSS						0.83	0.77 (0.26 - 0.90)	[31,41,43,45-49,55,57-60,70]
BDI							0.63 (0.44 - 0.90)	[31,39,46,53,59,63,64,67,68]

D. PREDICTIVE VALIDITY

	Sensitivity	Specificity	Cut-off value	References
BPRS-D	-	-	-	-
PANSS-D	78% (74- 81%)	85% (79-90%)	≥ 5; ≥ 10	[49,59]
HAMD	79% (67- 91%)	83% (81-84%)	≥ 12	[49,59]
MADRS	81%	81%	≥ 11	[49]
CDSS	88% (67-100%)	88% (74-97%)	≥ 5; ≥ 6; ≥ 9	[31,43,45,49,59]
BDI	72%	77%	≥25	[59]

a) Reliability was expressed by mean Cronbach's alpha and ICC values; n.a. = not applicable.
b) Mean correlation (R^2) with either a negative symptom scale or extra-pyramidal symptoms rating scale.
c) Average correlation for each comparison of two depression instruments and the pooled mean correlation indices for each instrument.
d) Mean sensitivity and specificity values at the optimal cut-off point.

SUMMARY OF RESULTS We identified five clinician-rated instruments and only one self-report with tested reliability and validity for the measurement of depressive symptoms in patients with schizophrenia.

RELIABILITY The reliability of the reviewed depression instruments was good in populations with schizophrenia and comparable to populations with depressed patients or healthy subjects.[20,86] In other words, patients with schizophrenia can reliably be assessed on the presence of depressive symptoms by interview or self-report.

VALIDITY The instruments differed in their accuracy to distinguish depressive symptoms from other symptoms of schizophrenia (divergent validity). Correlation studies and factor analysis showed that the CDSS measures nearly no other symptoms of schizophrenia. Inspection of the items of the CDSS supported that the overlap with negative symptoms or EPS was minimal compared to the other depression instruments. The high divergent validity of the CDSS is in line with the fact that this instrument has especially been developed for this population.[31] For example, "lack of interest" was not included, as this is both a symptom of depression and part of the negative symptoms of schizophrenia.[23,30,87] Divergent validity of the other (older) instruments may be hampered as they are based on several items about anxiety or somatic concern,[88] albeit anxiety-like symptoms do not belong to the current DSM-IV diagnostic criteria for depression.[88]

This wide variation of symptom dimensions covered by the reviewed instruments may explain the modest inter-correlations between most depression instruments. The low concurrent validity between instruments may even be over-estimated by the halo-effect. Ideally raters are not influenced by knowledge of the subject's scores on other instruments.[89] However, in some studies multiple instruments for depressive symptoms were rated by a single rater,[57] or the distribution of tasks among raters was unclear.[59,60]

The sensitivity and specificity to detect cases of depression in schizophrenia was highest for the CDSS, even though the CDSS did not cover all diagnostic criteria for depression as outlined above. Among the relatively scarce reports of predictive validity

we noticed inconsistencies in the reported cut-off values for the PANSS-D and CDSS. Nevertheless we were able to compare the instruments on their predictive validity as we included only those studies with standardized procedures to obtain the optimal cut-off value (Area Under the Curve methods).

PRACTICAL CONSIDERATIONS Practical issues such as time investment may also be important when choosing an instrument, apart from the psychometric aspects discussed above. The amount of training and time to complete the interview of the CDSS was comparable to the HAMD and MADRS. In contrast, the multidimensional instruments BPRS and PANSS may need more time and training to complete the interview, although an advantage may be that besides depressive symptoms, other psychotic symptoms can be evaluated at the same time.

FUTURE RESEARCH An important finding was the lack of self-report instruments for the measurement of depressive symptoms in this population. The concurrent and predictive validity of the only reviewed self-report here BDI was rather poor. Especially for routine outcome monitoring of depressive symptoms in clinical practice, self-report may save time and costs compared to a clinical interview. Although filling out questionnaires may be difficult for patients with considerable cognitive problems[31,70,90] and observable signs of depression could be missed by self-report,[13] self-report may provide more independent information on the patients' experience of depression in schizophrenia than interview-based assessments.[69] The literature search identified several other self-report questionnaires for depressive symptoms, such as the CES-D and the BSI (a short version of the Symptom Checklist-90).[33] Evaluation of the composition of the BSI showed that only one of the six items of the depression subscale had potential overlap with negative symptoms [data not shown]. Future research is needed to develop and validate a self-report comparable to the CDSS with respect to reliability and validity in schizophrenia.

RECOMMENDATIONS AND CONCLUSIONS In most of the reviewed studies the CDSS outperformed other depression instruments in terms of reliability and validity in patients with schizophrenia. Nevertheless the other depression instruments are still applied in schizophrenia research.[67,91-94] This is in accordance to a survey under

psychiatrists demonstrating the popularity of the HAMD, BDI and BPRS-D in daily practice.[95] The current review may aid clinicians and researchers to choose a well-validated instrument that selectively measures the symptoms of interest.

In summary, the CDSS was most reliable and valid for the measurement of depressive symptoms of schizophrenia. We recommend to use the CDSS in research as well as in daily clinical practice. Patients with a high score should be re-assessed using a diagnostic interview. As self-report is more expedient for the use in routine clinical practice, further research is needed to develop a self-reporting instrument with psychometric properties comparable to the CDSS.

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4

Psychometric properties of the self-report version of the Quick Inventory of Depressive Symptoms (QIDS-SR$_{16}$) questionnaire in patients with schizophrenia

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BACKGROUND Self-report instruments for the assessment of depressive symptoms in patients with psychotic disorders are scarce. The Quick Inventory of Depressive Symptoms (QIDS-SR$_{16}$) may be a useful self-report instrument, but has received little attention in this field.

OBJECTIVES To test the psychometric properties of the QIDS-SR$_{16}$ questionnaire in patients with a psychotic disorder.

METHODS Patients diagnosed with a psychotic disorder from health care institutions in The Netherlands were included in the study. Depressive symptoms were assessed with the QIDS-SR$_{16}$ and the Calgary Depression Scale for Schizophrenia (CDSS). Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) and extrapyramidal symptoms (EPS) with three EPS rating scales. Spearman's correlation coefficients were used to compare the total score of the QIDS-SR$_{16}$ with the total scores of the CDSS, PANSS-subscales and EPS rating scales.

RESULTS In a sample of 621 patients with psychotic disorders, the QIDS-SR$_{16}$ showed good internal consistency (α=0.80). The QIDS-SR16 correlated moderately with the CDSS (r=0.44) and the PANSS subscale for emotional distress (r=0.47). The QIDS-SR$_{16}$ showed weak correlation with the PANSS subscale for negative symptoms (r=0.28) and minimal correlation with EPS rating scales (r=0.09-0.16).

CONCLUSIONS The QIDS-SR$_{16}$ may reliably assess depressive symptoms in patients with psychotic disorders, but its concurrent validity with the CDSS was rather poor in this population. We would recommend developing a new self-report questionnaire for the assessment of depressive symptoms in patients with psychotic disorders.

Depressive symptoms are highly prevalent in patients with schizophrenia, with prevalence rates estimated between 7% and 75%.[1,2] Depressive symptoms are present throughout all phases of the illness,[3] and may lead to a higher burden of disease and more frequent relapses.[4,5] Screening and routine monitoring of these symptoms may guide appropriate treatment.[6,7] Depressive symptoms can be difficult to distinguish from negative symptoms and extrapyramidal symptoms (EPS), such as drug-induced parkinsonism.[8] Therefore, monitoring depressive symptoms requires reliable instruments with tested validity in patients with schizophrenia. To date, the only instrument designed for the assessment of depressive symptoms in this patient population is the interview-based Calgary Depression Scale for Schizophrenia (CDSS).[9] The CDSS is a reliable and valid instrument that is able to distinguish depressive symptoms from negative psychotic symptoms and EPS.[9] However, the interview-based assessment method has some drawbacks, such as the need for trained interviewers and observer bias. Self-report may be as good as interview-based assessments for monitoring change in psychopathology,[10] and saves time and costs in routine clinical practice.[11] The availability of self-report depression instruments with comparable reliability and validity in patients with schizophrenia is however limited.[12] The Quick Inventory of Depressive Symptoms (QIDS-SR_{16}) is a short and easy-to-use self-report instrument to assess depressive symptoms.[13] The QIDS-SR_{16} is sensitive to symptomatic change and its psychometric properties are good in patients with depressive disorders.[14] Furthermore, it was found that the presence of psychotic symptoms did not meaningfully affect the ability of self-rating to recognize depressive symptoms in patients with major depressive disorder.[15] To our knowledge, the reliability and validity of the QIDS-SR_{16} has not been tested in patients with schizophrenia. A question of specific interest is whether the QIDS-SR_{16} can distinguish depressive symptoms from negative and extrapyramidal symptoms in this population (divergent validity). Furthermore, it is unknown whether the latent structure of the QIDS-SR_{16} remains one-dimensional,[16,17] or that multiple (negative symptom) dimensions can be identified when applied in patients with schizophrenia.

The aim of the current study is to evaluate the psychometric properties of the QIDS-SR_{16} in a population of patients with psychotic disorders. We examined (1) the internal consistency of the QIDS-SR_{16}, (2) the dimensional structure, (3) the concurrent validity with other depression instruments and (4) the divergent validity with negative and extrapyramidal symptoms.

SUBJECTS Subjects were patients participating in the Genetic Risk and Outcome of Psychosis (GROUP) study, a naturalistic longitudinal cohort study. The longitudinal GROUP study is conducted by four academic centers in the Netherlands and a large number of mental health institutes in the Netherlands and the Dutch speaking region of Belgium. The GROUP study was approved centrally by the Ethical Review Board of the University Medical Center Utrecht and all participants gave written informed consent in accordance with the committee's guidelines. For a detailed overview of the GROUP structure, data flow, quality control, recruitment, sample characteristics of the studied patients and training procedures of the assessors, see Korver (2012).[18] The current data was collected during the second assessment of the study, three years after the baseline assessment (GROUP data release 3.02). Patients were included in the current study if they had a diagnosis of a psychotic disorder according to the DSM-IV criteria,[19] and if data of the following rating scales were complete: the Quick Inventory of Depressive Symptoms (QIDS-SR$_{16}$), Calgary Depression Scale for Schizophrenia (CDSS), Positive and Negative Syndrome Scale (PANSS), Abnormal and Involuntary Movements Scale (AIMS) and Barnes Akathisia Rating Scale (BARS). These rating scales were administered by trained research assistants.

MEASURES Patients completed the self-report version of QIDS-SR$_{16}$ to assess depressive symptoms.[13] The measure consists of 16 items, covering nine depressive symptom domains. Each domain score is based on the highest score on the pertaining items. Domain scores and item scores are rated on a Likert scale ranging from 0 to 3, with a total score range of 0–27. For an interpretation the QIDS-SR$_{16}$ total score see http://www.ids-qids.org. Depressive symptoms were also assessed by the 9-item CDSS interview.[9] Item scores are rated on a Likert scale ranging from 0 to 3. A sum score above 4 out of 27 on the CDSS was used as cut-off scores to establish the presence of a minor depressive episode or clinical depression.[9,20] Psychotic symptoms were assessed with the PANSS.[21,22] For the current analyses, we used the five-factor model of the PANSS,[23] consisting of the subscales 'positive symptoms', 'negative symptoms', 'disorganization symptoms', 'excitement' and 'emotional distress'. Item scores of the PANSS range from 1 (not present) to 7 (extreme) and the subscales scores for negative symptoms range from 7-49 and 7-28 for emotional distress. Extrapyramidal symptoms were assessed using the AIMS,[24] the BARS,[25] and, when available, the 'motor examination' subscale of the Unified Parkinson's Disease Rating Scale (UPDRS).[26] The CDSS, the PANSS and the EPS rating scales were assessed by

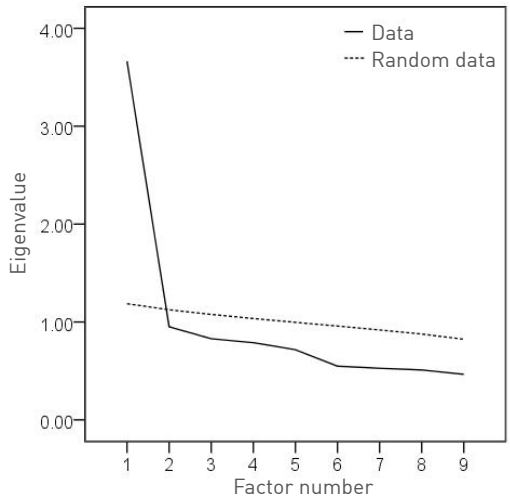
the same research assistant.

STATISTICAL ANALYSES Psychometric properties of the QIDS-SR_{16} were examined using SPSS, version 16.0. The reliability of the QIDS-SR_{16} was assessed by calculating Cronbach's alpha as a measure for internal consistency. A value of 0.80 or higher indicated good internal consistency.[27] Additionally, inter-item correlations of the QIDS-SR_{16} were calculated. Average values of $r>0.15$ were deemed acceptable, since depressive symptoms as covered by the QIDS-SR_{16} may represent a broad construct.[28] The dimensional structure of the QIDS-SR_{16} was examined by parallel analysis, a form of exploratory factor analysis, using principal component analysis (PCA).[29] In parallel analysis, the factors are retained as long as the *i*th eigenvalue from the actual data is greater than the *i*th eigenvalue extracted from a random dataset, generated to parallel the actual dataset in number of cases and variables. The total score of the QIDS-SR_{16} was compared with the scores on the CDSS, PANSS and EPS rating scales. Concurrent validity was investigated by calculating correlations of the QIDS-SR_{16} with the CDSS and the PANSS subscale for emotional distress. Divergent validity was examined by correlations of the QIDS-SR_{16} with the PANSS-Negative symptoms subscale and the three EPS rating scales. Taking into account the non-normal distribution of the data, we used Spearman correlations for all these analyses.

SAMPLE Overall, 809 (72%) of the 1119 patients with a psychotic disorder who presented at baseline participated in the second assessment. Patients who participated in the second assessment did not differ in age (F[1,1117]=3.15; p=0.076), gender (x^2[1]=0.71; p=0.40) or duration of illness (F[1,1032]=3.26; p=0.071) from those who only completed baseline assessment. Of the 809 patients who participated in the second assessment, 621 patients completed all questionnaires (QIDS-SR_{16}, CDSS, PANSS, AIMS and BARS) required for inclusion in the current study. Demographic and clinical descriptive information of this sample can be found in Table 1. According to the CDSS, clinical depression or a minor depressive episode was present among 17% (N=103) of the patients.

RELIABILITY AND DIMENSIONALITY The QIDS-SR_{16} showed good internal consistency (Cronbach's alpha= 0.80). All individual inter-item correlations were within an acceptable range of 0.16-0.52, with a mean inter-item correlation of 0.29. The QIDS-SR_{16} was represented by one underlying factor in this sample (Figure 1).

FIGURE 1. Scree plot of obtained eigenvalues of the QIDS-SR_{16}, compared to eigenvalues based on random data.



Ad Table 1: Abbreviations: SD, Standard Deviation; QIDS-SR_{16}, Quick Inventory of Depressive Symptomatology 16-item self-report version; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale and UPDRS, Unified Parkinson's Disease Rating Scale. *Data on antipsychotic medication was missing for n=140 (23%) patients; **UPDRS ratings were missing for n=90 (14%) patients.

TABLE 1. Patient characteristics (N=621).

	Total N=621 Mean (SD; range) or N (%)
Age	30.1 (7.3; 18-59)
Male (%)	478 (77%)
Education	
Primary school	39 (6%)
Secondary school/high school	322 (52%)
Vocational education	150 (24%)
Vocational higher education	65 (11%)
University	45 (7%)
Illness duration (years)	7.3 (4.1; 2.0-43.1)
Age of onset first psychosis (years)	22.3 (6.7; 5-51)
Primary diagnosis	
Schizophrenia	398 (64%)
Schizoaffective disorder	80 (13%)
Schizophreniform disorder	37 (6%)
Delusional disorder	14 (2%)
Brief psychotic disorder	13 (2%)
Psychotic disorder NOS	64 (10%)
Other psychotic disorder	15 (2%)
Antidepressants	81 (13%)
Antipsychotics*	
No antipsychotics	67 (11%)
Risperidone	58 (9%)
Olanzapine	91 (15%)
Quetiapine	28 (5%)
Clozapine	71 (11%)
Haloperidol	16 (3%)
Aripiprazol	50 (8%)
Other antipsychotics	35 (6%)
Combination therapy	65 (10%)
QIDS-SR_{16} (total)	6.6 (4.9; 0-26)
Sleep disturbance	1.8 (0.9; 0-3)
Depressed mood	0.7 (0.8; 0-3)
Change in appetite or weight	0.9 (1.0; 0-3)
Concentration/decision making	0.6 (0.8; 0-3)
Self-view	0.7 (1.1; 0-3)
Suicidal ideation	0.3 (0.7, 0-3)
Interest	0.4 (0.8, 0-3)
Energy/fatigue	0.6 (0.8; 0-3)
Psychomotor agitation/retardation	0.7 (0.9; 0-3)
CDSS (total)	2.0 (2.8; 1-16)
PANSS Total	61.8 (18.9; 41-148)
PANSS-EMO (emotional distress)	13.1 (4.8; 8-33)
PANSS-NEG (negative symptoms)	12.6 (5.4; 4-41)
PANSS-POS (positive symptoms)	11.3 (5.4; 3-39)
PANSS-DIS (disorganized symptoms)	14.2 (5.1; 10-46)
PANSS-EXC (excitement symptoms)	10.6 (3.2; 2-29)
AIMS (total)	0.1 (0.2; 0-1.9)
BARS (total)	0.3 (0.6; 0-4.0)
UPDRS (subtotal motor symptoms)**	0.2 (0.1; 0-1.4)

CONCURRENT AND DIVERGENT VALIDITY The correlations of the individual domains of the QIDS-SR$_{16}$ with the CDSS ranged between 0.14 and 0.46 (Table 2). The total score of the QIDS-SR$_{16}$ correlated moderately with the CDSS (ρ=0.44; p<.001) and the PANSS subscale for emotional distress (ρ=0.47; p<.001), as displayed in Table 3. The QIDS-SR$_{16}$ showed weak correlations with negative symptom ratings of the PANSS (ρ=0.28; p<.001) and extrapyramidal symptom ratings of the AIMS (ρ=0.09; p<.05), BARS (ρ=0.16; p<.001) and UPDRS-motor subscale (ρ=0.13; p<.001).

TABLE 2. Correlation of QIDS-SR$_{16}$ symptom domains with the CDSS total score.

QIDS-SR$_{16}$ domains	Correlation
Sleep disturbance	0.22
Depressed (sad) mood	0.46
Change in appetite or weight	0.14
Concentration/decision making	0.27
Self-view	0.36
Suicidal ideation	0.38
Interest	0.33
Energy/fatigue	0.28
Psychomotor agitation/retardation	0.28

All correlations were significant (p<.001). Abbreviations: QIDS-SR$_{16}$, Quick Inventory of Depressive Symptoms 16-item self-report version; CDSS, Calgary Depression Scale for Schizophrenia.

TABLE 3. Concurrent validity of the QIDS-SR$_{16}$ total score with other depression instruments and divergent validity with negative symptoms and extrapyramidal symptoms.

		QIDS-SR$_{16}$	CDSS	PANSS-D
Concurrent validity	QIDS-SR$_{16}$	1		
	CDSS	0.44***	1	
	PANSS-D	0.47***	0.59***	1
Divergent validity	PANSS-N	0.28***	0.34***	0.40***
	AIMS	0.09*	0.06	0.06
	BARS	0.16***	0.09*	0.15***
	UPDRS-motor	0.10*	0.17***	0.21***

Significant correlations were indicated by ***= p <.001; **= p <.01; *= p<.05. Abbreviations: QIDS-SR$_{16}$, Quick Inventory of Depressive Symptoms 16-item self-report version; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale, emotional distress subscale (-D) and Negative symptom subscale (-N); AIMS, Abnormal and Involuntary Movements Scale; BARS, Barnes Akathisia Rating Scale and UPDRS-motor, Motor subscale of the Unified Parkinson's Disease Rating Scale.

The current study was, to the best of our knowledge, the first to investigate the psychometric properties of the QIDS-SR_{16} in a large sample of patients with psychotic disorders. The QIDS-SR_{16} remained unidimensional in the current sample.[16,17] Furthermore, the internal consistency of the QIDS-SR_{16} was good in our patient population, and comparable to that previously reported for the CDSS.[30] This suggests that patients with a psychotic disorder are able to rate their depressive symptoms in a reliable way.[10] However, the QIDS-SR_{16} agreed moderately with the CDSS, suggesting conceptual differences with the gold standard rating scale (CDSS) for depressive symptoms in patients with schizophrenia.

These conceptual differences may reflect differences in item selection between the QIDS-SR_{16} and the CDSS. Unlike the CDSS, the QIDS-SR_{16} is not specifically designed to assess depressive symptoms in patients with psychotic disorders. Especially the QIDS-SR_{16} symptom domains on 'sleep' and 'appetite' showed low agreement with the CDSS in our study. The scores on the sleep domain were relatively high compared to other domains of the QIDS-SR_{16}; this was in most cases driven by the item 'excessive sleep' (data not shown). Excessive sleep and increased appetite may reflect side effects of antipsychotics,[31,32] and hence not necessarily be related to the 'physical' symptoms of depression.[19] Indeed, post hoc analysis demonstrated that those patients using antipsychotics with high antagonistic affinity for the histamine receptor (olanzapine or clozapine) reported higher scores on excessive sleep than patients using other antipsychotics (OR [95%CI] = 1.88 [1.31-2.68]; data not shown). Similarly, patients using olanzapine or clozapine were more likely to report increased appetite (OR [95%CI] = 1.94 [1.28-2.95]; data not shown). It can be argued that antipsychotic side effects confounded changes in sleep and appetite as measured by the QIDS-SR_{16} in the current sample. In contrast, the CDSS measures 'early awakening' and 'morning depression' as a proxy for the physical symptoms of depression, in a way less sensitive to confounding by antipsychotic side effects. Another conceptual difference is that the CDSS and other self-report questionnaires like the Center of Epidemiologic Studies-Depression,[33] but not the QIDS-SR_{16}, cover hopelessness. Patients with schizophrenia may be prone to psychological depressive symptoms like hopelessness and self-depreciation, possibly related to demoralization in response to the severe mental illness.[34] Thus careful item selection targeting only those depressive symptoms specific for patients with a psychotic disorder may be relevant for the validity of a self-report depression instrument in this population.

Although there was some overlap, the QIDS-SR$_{16}$ discriminated depressive symptoms from negative symptoms in an acceptable way, in line with previous work on the full 30-item Inventory of Depressive Symptoms (IDS) in a mixed population of patients with schizophrenia and bipolar disorder.[35,36] In addition, a latent factor for negative symptoms was not identified for the QIDS-SR$_{16}$, despite that several items overlap with negative symptoms, such as of concentration difficulties (question #10), lack of interest (#13) and lack of energy (#14). The current results suggest that, although the QIDS-SR$_{16}$ may partly tap into the negative symptom dimension and thus should be interpreted with care, its divergent validity is acceptable in patients with psychotic disorders.

An unexpected result is the relatively high correlation of the CDSS with negative symptoms in comparison to previous reports of the CDSS in patients with schizophrenia.[12] Though some correlation with negative symptoms is acceptable, as patients may often experience both negative and depressive symptoms at the same time.[37] Another caveat when interpreting the current results is that the majority of the patients had low EPS ratings. The relatively young and possibly well stabilized sample of patients may explain the rare presence of EPS, as previously described for the baseline measurement of the current sample.[38] We therefore remain inconclusive about the divergent validity of the QIDS-SR$_{16}$ with respect to the extrapyramidal symptoms in this population.

Important strength of the study is its large sample size. A limitation of the study design may be that the same research assistant rated both the CDSS and the PANSS interview. This may have led to an overestimation of the correlation between the CDSS and the PANSS subscale for emotional distress, because of prior knowledge of the raters based on the previous interview. Therefore, the PANSS subscale for emotional distress does not necessarily outperform the QIDS-SR$_{16}$ on its concurrent validity with the CDSS.

To conclude, we showed that patients with a psychotic disorder can reliably rate their depressive symptoms by means of the self-report. However, based on the poor concurrent validity of the QIDS-SR$_{16}$ with the CDSS, the gold standard for rating depression in patients with schizophrenia, we would not recommend applying the QIDS-SR$_{16}$ for the assessment of depressive symptoms in this population. Future research may focus on the development of a new self-report instrument, especially designed to assess depressive symptoms in patients with psychotic disorders.

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5

Validity of the Center for Epidemiologic Studies-Depression scale in patients with schizophrenia

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BACKGROUND Self-report instruments for the assessment of depressive symptoms in patients with schizophrenia are scarce. The Center for Epidemiologic Studies-Depression (CES-D) may be a useful self-report instrument, but has received little attention in this field of research.

OBJECTIVE We aimed to test the concurrent validity between the self-reported CES-D and the Calgary Depression Scale for Schizophrenia (CDSS) interview in patients with schizophrenia.

METHODS Included were patients with schizophrenia who were interviewed with CDSS and completed the CES-D as part of routine outcome monitoring in one center in the Netherlands. The Spearman's rank correlation coefficient was used to compare the total score of the CES-D with that of the CDSS.

RESULTS In a sample of 122 patients with schizophrenia, the correlation between the CES-D and CDSS was 0.703.

CONCLUSIONS Self-rating of depression by means of the CES-D seems to be adequate for assessing and monitoring depressive symptoms in patients with schizophrenia. A limitation was that we could not compare the predictive performance of the CES-D with the CDSS.

The prevalence of depressive symptoms in patients with schizophrenia is high (about 25%).[1] Depressive symptoms are present throughout all phases of the illness. They are associated with a high burden of disease, as well as frequent relapses.[2,3] Screening and routine monitoring of these symptoms may guide appropriate treatment.[4,5] Depressive symptoms are difficult to distinguish from negative psychotic symptoms and other symptoms of schizophrenia, requiring instruments with tested validity in patients with schizophrenia. To date, the only instrument designed for the assessment of depressive symptoms in this patient population is the interview-based Calgary Depression Scale for Schizophrenia (CDSS).[6] Self-report in routine clinical practice is much less time-consuming and expensive than an interview-based assessment. Furthermore, self-report may provide more independent information on the patients' experience of depression in schizophrenia,[7] and support shared decision making with the patient. We recently demonstrated that not all self-report depression instruments can validly be applied in patients with schizophrenia.[8] The Beck Depression Inventory (BDI)[9] is the only self-report instrument for depressive symptoms of which several aspects of reliability and validity have been tested in patients with schizophrenia.[10] The predictive validity to detect cases of depression in patients with schizophrenia of the BDI is, however, poor.[10] Furthermore, about 10% of patients has difficulties to complete this questionnaire.[11,12] Especially those patients with concentration problems associated with schizophrenia may find it easier to rate their depressive symptoms on a Likert scale with a visual degree of severity, such as the Center for Epidemiologic Studies-Depression (CES-D).[13]

The CES-D is a short self-report questionnaire designed to detect depressive symptoms in the general population.[13] The CES-D discriminates depressive symptoms from negative symptoms in patients with schizophrenia,[14] and the predictive validity of the CES-D has been shown to be sufficient to detect cases of depression in patients with schizophrenia (91% sensitivity, 79% specificity).[15] The performance of the CES-D has been compared with the Hamilton Depression Rating Scale (HAMD) and the Depression-subscale of the Brief Psychiatric Rating Scale (BPRS),[14] which both appeared to have less validity in patients with schizophrenia compared to the CDSS.[10] To our knowledge the CES-D has not been compared with the CDSS. In the current study we aimed to test the concurrent validity between the CES-D and the CDSS for the assessment of depressive symptoms in patients with psychotic disorders. Additionally the CES-D was compared with the depression item of the Health of Nations Outcome Scale (HoNOS) for general health and functioning.

This cross-sectional study was carried out between February 2010-2011 in the department of psychotic disorders of a mental health care organization in the North of the Netherlands, as part of the PHArmacotherapy Monitoring and OUtcome Study (PHAMOUS).[4,16] We included all patients of 18 years and older, with diagnosed schizophrenia or related psychotic disorders according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV-codes 295.4 - 295.9, 297.1, 298.8 and 298.9).[17] Patients had given informed consent in accordance with the latest version of the Declaration of Helsinki. Patients rated their depressive symptoms by completing the 20-item CES-D questionnaire, prior to the nine-item semi-structured CDSS interview by a trained nurse. A psychiatrist assessed psychosocial functioning using the Global Assessment of Functioning scales (GAF-Symptoms and GAF-Disability)[17] and the Health of Nations Outcome Scale (HoNOS).[18] Current medication use was retrieved from the patient's medical records and was then confirmed with the patient.

A sum score above 15 out of 60 on the CES-D[19] and a sum score above 4 out of 27 on the CDSS[6,20] was used as cut-off score to establish the presence of a minor depressive episode or clinical depression. All questionnaires have been translated into Dutch by a bilingual psychiatrist and the English back-translated versions were corrected by the author of the original version.[6,21,22] The total score of the CES-D was compared with the total score and the score on the 9 individual items of the CDSS. Both the CES-D and the CDSS were additionally compared with the depression-item of the HoNOS.

The level of agreement between depression instruments was expressed by the Spearman's rank correlation coefficient. As a measure of reliability, we determined the internal consistency by the Cronbach's alpha (α) for each questionnaire. The internal consistency is the extent to which items refer to the concept (here depression). All p-values were two-sided and a probability level of $p<0.05$ was accepted as statistically significant.

Of the 139 patients diagnosed with schizophrenia or related psychotic disorders, 16 patients refused the CDSS interview and one patient did not complete the CES-D questionnaire. So a total of 122 patients were included in the study. The mean age was 41.1 years (SD 11.0; range 18-66 years) and 67% (n=82) were male patients. The mean GAF-score was 60.0 (SD 14.5) for symptoms and respectively 60.3 (SD 12.9) for disability. Antidepressants were prescribed for 33% (n=40) of the patients and mood stabilizers for 5% (n=6) in addition to their antipsychotic treatment. Of note, information on patient status, GAF, HoNOS and current medication use was lacking for 14 patients. Clinical depression was present among 37.7% (n=46) of the patients according to the CES-D and 9.8% (n=12) according to the CDSS, of which 11 cases were also detected by the CES-D.

The CES-D correlated with individual items of the CDSS between 0.197 and 0.527 (Table 1). The correlation coefficient between the total scores of the CES-D and the CDSS was 0.703 ($p<0.01$). The correlation of the CES-D and CDSS with the depression item of the HoNOS was respectively 0.495 ($p<0.01$) and 0.418 ($p<0.01$). The internal consistency of the CES-D (α=0.91) was superior to the CDSS (α=0.68).

The total score obtained by self-rated depressive symptoms by the CES-D agreed well with the total score of the observer-rated CDSS. The internal consistency of the CES-D was high, in line with previous reports of the CES-D.[13,14] On individual item level, the CES-D agreed best with the depressive mood component of the CDSS. This may reflect the unidimensional emphasis on the depressed mood (affective) component of the CES-D.[13] The CES-D is primarily designed to measure changes in the severity of sub-clinical depressive symptoms over time.[13,23] Therefore the CES-D does not cover all nine diagnostic criteria for a clinical depression (e.g. guilt),[17] like the HAMD[24] and the Montgomery-Åsberg Depression Rating Scale (MADRS).[25] The upcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) advocates to measure psychopathology in terms of quantitative dimensions, rather than solely as discontinuous diagnostic categories (http://www.dsm5.org). The CES-D could be a useful instrument to monitor the gradual severity of depressive symptoms over time, as it has shown to be sensitive to detect symptomatic changes over time in depressed patients.[26]

The agreement between the CES-D and the CDSS was comparable to the concurrent validity of the BDI with other depression instruments in patients with schizophrenia (correlation coefficients r›0.70).[6,27,28] In the current study, we noticed that patients experienced minimal effort to complete the CES-D questionnaire, implying that this self-report instrument is feasible in a population with schizophrenia. Furthermore, the relatively poor congruency of both the CES-D and CDSS with the HoNOS-depression item indicated that a single observed-rated depression item of a general health assessment scale in this population is not adequate in detecting a range of depressive symptoms.

The prevalence rate of potential cases of depression according to the CES-D appeared to be higher than the CDSS. This could imply that the CES-D is less specific to detect cases of depression (more false positives) than the CDSS, which is reasonable since the CES-D was primarily developed to monitor sub-clinical depressive symptoms rather than detecting cases of depression. Another reason for the high prevalence rate could be that the cut-off score of the CES-D to detect cases of depression was not optimal for the current population. For example, the prevalence of potential cases of depression drops to 19% when using a cut-off score of ›24 (data not shown), as recommended by Cho and Kim (1998) for use of the Korean version of the CES-D in psychiatric patients.[15] As a limitation of the current study, we could not determine

the exact prevalence of depression in our sample, as depression diagnoses were not systematically recorded in the current study. Future research is needed to determine an optimal cut-off score to predict cases of depression by the CES-D in patients with schizophrenia. We therefore recommend careful interpretation of positive CES-D scores and confirm the diagnosis of depression in patients with persistently high scores by a diagnostic interview.

The current study demonstrated that the CES-D is a feasible self-report instrument for the monitoring of depressive symptoms in routine clinical practice with high internal consistency and concurrent validity with other depression instruments in patients with schizophrenia.

TABLE 1. Correlation of the total score of the CES-D with the CDSS items and total score (Spearman's rank correlation, * $p<0.05$; ** $p<0.01$).

	CDSS-item	Correlation coefficient
1	depression	.527**
2	hopelessness	.382**
3	self-depreciation	.265**
4	guilty ideas of reference	.197*
5	pathological guilt	.211*
6	morning depression	.470**
7	early waking up	.278**
8	suicidal ideas	.364**
9	observed depression	.199*
	Total CDSS-score	.703**

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A brief version of the Subjects' Response to Antipsychotics questionnaire to evaluate treatment effects

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BACKGROUND Monitoring the patients' experiences with antipsychotics may help to improve medication adherence and outcome. We aimed to develop a shorter version of a comprehensive 74-item self-report questionnaire suitable for routine monitoring of desired and undesired effects of antipsychotics.

METHODS Included were patients with psychotic disorders from seven mental health care organizations in the Netherlands, using antipsychotic medication, who completed the Subjects' Response to Antipsychotics (SRA-74). Exploratory factor analysis (EFA) and similarity analysis based on mutual information were used to identify the latent factor structure of the SRA. Items were reduced according to their metric properties and clinical relevance upon consensus by an expert panel, using a Delphi procedure of three rounds. We determined the internal consistency of the shorter version using Cronbach's alpha.

RESULTS SRA data of N=1478 patients (mean age of 40 years, 31% females) were eligible for analysis. EFA extracted thirteen factors from the SRA-74, including four factors for desired effects (e.g. recovery of psychosis, cognition and social functioning) and nine factors for undesired effects (e.g. weight gain, flattened affect and increased sleep). Based on this solution 12 items were eliminated for statistical reasons. The expert panel eliminated another 28 items with redundant content, resulting in a 34-item version. The SRA-34 includes 10 desired and 24 clinically relevant undesired effects. Both the subscale for desired and undesired effects have a Cronbach's alpha coefficient of 0.82.

CONCLUSIONS The SRA-34 can be used to evaluate desired and undesired effects of antipsychotics in routine clinical practice and research.

Schizophrenia is a chronic psychiatric disease, commonly necessitating lifelong treatment with antipsychotics. Antipsychotics increase the burden of disease, when they affect patients' physical, psychological, sexual and social functioning.[1] The patients' experience of desired and undesired effects in response to antipsychotic medication has been identified as a strong predictor of adherence and outcome.[2,3] Systematic monitoring of the balance between desired and undesired effects with antipsychotics is important for disease management.[4,5] This requires a reliable and valid instrument.

Self-report is most optimal for the detection of often neglected, yet disturbing experiences, such as sexual side effects.[6,7] Furthermore, self-report may save time and costs in routine clinical practice. Existing self-rating scales assessing experiences of antipsychotics focus on quality of life, like the Subjective Well-being on Neuroleptics (SWN)[8] or undesired effects only, like the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)[9] and the Glasgow Antipsychotic Side-effect Scale (GASS),[10] see Wolters.[11] In contrast, the Subjects' Response to Antipsychotics (SRA) is a comprehensive assessment of 74 desired and undesired effects attributed to antipsychotic medication, divided over 8 subscales.[12] It is constructed of lay term expressions, based on original patient statements which may be easier understood than some of the clinical terms in the LUNSERS.[10] However, our own experience with the SRA-74 suggests that especially patients with concentration difficulties find it a long questionnaire with many questions addressing the same clinical effect. Reducing the total number of items with in the range of other scales (about 30 items)[8,9] would increase its feasibility for screening purposes. The subscale structure of the SRA-74 has been established by a priori assumptions.[12] So far, the latent structure has not been evaluated using more advanced statistical methods. The current study therefore explored the latent structure of the SRA by exploratory factor analysis (EFA) in a large cohort of patients with psychotic disorders. The main aim was to develop a shorter version of the SRA, while maintaining the latent structure.

QUESTIONNAIRES The SRA-74 consists of one subscale of 24 desired effects, seven subscales of 30 undesired effects of antipsychotics and 20 miscellaneous undesired effects not belonging to a subscale.[12] The subscales have good internal consistency (Chronbach's alpha 0.69-0.93) and test-retest reliability (Pearson's r correlation 0.39-0.60). The SRA is rated on a 3-point scale (not present / yes, mild / yes, severe). Patients received the SRA by mail to complete it at home. In case of difficulties to complete the questionnaire they received help from a trained nurse.

Trained nurses rated the level of psychotic symptoms using the Positive and Negative Symptom Scale for Remission (PANSS-R).[13] The patient's psychiatrist or case manager rated psychosocial functioning using the Global Assessment of Functioning scale (GAF; DSM-IV).[14] A psychiatrist diagnosed each patient according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) classification system.[14] Medication use over the past year was retrieved from medical records and confirmed with the patient.

SUBJECTS Patients with psychotic disorders receiving mental health care in the North of the Netherlands, Amsterdam and Dordrecht were invited to participate in the annual screening of their mental and physical health by the Pharmacotherapy Monitoring and Outcome Survey (PHAMOUS). Investigations were carried out between 2006 and 2010, in accordance with the latest version of the Declaration of Helsinki. Included were patients with psychotic disorders (DSM-IV codes 295.4 - 295.9, 297.1, 298.8 and 298.9), who used antipsychotics for at least one month and completed the SRA (maximally 2 items missing). In case a patient had participated in successive annual assessments, the first available measurement was selected for evaluation.

LATENT STRUCTURE Exploratory factor analysis (EFA) was used to identify the latent factor structure of the SRA-74. Since one item of the SRA (about menstruation) was only completed by female participants, factor analysis was conducted on 73 items. In addition to EFA, we performed similarity analysis to visualize the latent structure of the SRA-74.

We used similarity analysis based on the amount of mutual information shared between items, according to Shannon's information theory.[15] In contrast to EFA, the estimates of mutual information are independent of the prevalence of responses, i.e. insensitive to the distribution of 'no'-responses. So far, mutual information has mainly been applied to analyze similarity in biomedical signals,[16] imaging and genotyping data,[17,18] but relatively scarce in psychometrics.[19,20]

The similarity matrix was composed of pair-wise mutual information for the responses on all 73 items, using the formula

$$I(X;Y) = \sum_{y \epsilon Y} \sum_{x \epsilon Y} p(x,y) \log \frac{p(x,y)}{p(x),p(y)}$$

where $p(x,y)$ is the frequency of (x,y) in the data, and $p(x)$ and $p(y)$ are the frequencies of x and y, respectively. Here x and y, are the outcomes of two items being compared. Mutual information $I_{(X;Y)}$ is a measure of similarity yielding values in the range of [0, ∞). Since the values of $I_{(X;Y)}$ are considered to have no obvious interpretation,[19] examination of the similarity matrix was data driven. Factors having at least two items sharing a relevant amount of mutual information were deemed reliable.

ITEM REDUCTION Within each factor, items with loadings r<0.30 on all factors, cross-loading r>0.30 on two or more factors, or loading on a factor with a low main factor loading of r<0.50 were considered non-factorable.[21] Non-factorable items were eliminated if there was no consensus about their clinical relevance by the expert panel (see below). Factorable items with high factor loadings (r>0.80) and/or a highly similar content within the same factor were considered redundant. Of each pair of redundant statements, the item with least specific, most ambiguous or multi-interpretable (e.g. feelings that can be interpreted both literal and metaphorical) content was eliminated upon consensus by the expert panel.

DELPHI PROCEDURE A Delphi procedure consisting of three consecutive rounds was used to reach consensus about the clinical relevance of the items in the questionnaire.[22] The expert panel, all native Dutch speaking, consisted of six psychiatrists, two neurobiologists and two psychologists. In the first round, the panelists received the full questionnaire including the results of the statistical analysis by e-mail. The experts were asked 1) to rank order the clinical relevance of the non-factorable items dropped for statistical reasons and 2) to mark redundant items

until maximally three items within each factor were retained. Clinical relevance was defined as being relevant for a patient to (dis)continue antipsychotic therapy. In the second round, the panelists received a new proposal for the shortened questionnaire, including a summary of the arguments for item elimination or preservation. The experts were asked whether they agreed with the proposed item reduction. If not, they were asked to replace redundant items and to re-rank the clinical relevance of each item. In the third and final round, consensus was reached about the final version of the questionnaire. Items with consensus rates of more than 75% agreement within the panel were retained.

STATISTICS Descriptive analyses and factor analysis were performed using Statistical Package for Social Sciences (PASW-18). Patient characteristics were compared between samples by Chi-Square tests for categorical variables and Mann-Whitney U tests for continuous variables. Missing SRA-responses were imputed for patients with maximally 2 items missing, using the default settings of the multiple imputation method and random number generator (Mersenne Twister) of PASW-18. Prevalence rates of SRA items were based on dichotomized scores (no/yes). Factor analysis was conducted on the original 3-point scale of the SRA. The responses on the desired effects were reversed prior to factor analysis to obtain uniform scaling. The extraction method for EFA was Generalized Least Squares. The rotation method was Direct Oblimin with Kaiser Normalization, assuming a certain degree of correlation between factors (e.g. *increased sleep* with *sedation*). The number of factors to be retained was predefined by the Kaisers criterion (eigenvalues ≥ 1). Kaiser-Meyer-Olkin (KMO) and Bartlett`s test for sphericity were calculated to test whether the relationships among variables in the sample are adequate for factor analysis.

The similarity between items within each factor in terms of mutual information was analyzed by loading all possible combinations of the 73 items as individual crosstabs into MATLAB Version 2011. Mutual information was calculated for all crosstabs using logarithms (the in-home created script is available on request) and visualized by a 73x73 similarity matrix. Items were grouped according to the factors from the EFA.

The internal consistency of the final version of the SRA was calculated for the factorable items within the desired effects subscale and undesired effects subscale. A Cronbach's alpha of $\alpha \geq 0.80$ indicates good internal consistency.[23]

SUBJECTS The number of patients included for evaluation was n=1478 (66%) out of n=2241 patients with psychotic disorders receiving routine outcome assessments in the selected mental health care organizations between 2006 and 2010. Excluded were n=142 (6%) patients not using antipsychotics at time of interview and n=621 (28%) of the patients having three or more SRA-items missing. There were no major differences between the patients who did not complete and who did complete the SRA questionnaire. In the included sample, no systematic patterns were observed among missing SRA-items and no items had more than 5% missing values. Hence 325 (0.3%) missing values were imputed for those patients with maximally 2 missing SRA-items. The included patients had a mean age of 40 (SD 11) years and consisted of n=462 (31%) females (Table 1). On average, patients attributed 13 (56%) out of 24 desired effects to antipsychotics, compared to 18 (38%) out of 50 undesired effects. Patients most frequently reported the desired effects of the SRA-74, including 'My emotions have returned' (93%), 'My memory has improved' (92%) and 'I am more active' (90%); most frequently reported undesired effects were 'I need more sleep' (62%), "My weight has increased'(60%) and 'I get physically tired more easily' (57%). All other statements had a prevalence rate above 5%.

TABLE 1. Patient characteristics (n=1478). Values were missing for the following variables: duration of illness (n=302; 14%), PANSS (n=75; 3%), GAF Symptoms (n=365; 17%) and GAF Functioning (n=544; 25%).

	Sample (n=1478)	
	N or mean	% or SD
Gender (female)	462	31%
Age (years)	40.1	11.4
Duration of illness (years)	13.9	9.9
PANSS-Positive	2.1	1.0
PANSS-Negative	2.3	1.1
GAF Symptoms	53.0	14.1
GAF Functioning	52.5	13.2
Inpatients	415	28%
Antipsychotics		
Haloperidol	83	6%
Risperidone	202	14%
Olanzapine	268	18%
Clozapine	186	13%
Quetiapine	104	7%
Aripiprazole	78	5%
Other antipsychotic	254	17%
Combinations	303	21%
Number of co-medications	2.0	2.2
Reported desired effects (of 24 items)	13	56%
Reported undesired effects (of 50 items)	18	37%

LATENT STRUCTURE Exploratory factor analysis extracted fourteen latent factors from the 73 SRA-items, explaining a total variance of 58% (Table 2). The correlation matrix of the data was considered factorable because the EFA solution passed the Kaiser-Meyer-Olkin (KMO) test with a value of ›0.60 and the Bartlett`s Test of Sphericity was significant (p‹0.001). All factors had high main factor loadings (0.58 – 1.00), except for factor 13 (0.31). Factor 13 consisted of items with heterogeneous content and low factor loadings.

Visual inspection of the similarity matrix gave comparable results as our exploratory factor analysis. All items with high factor loadings shared a relevant degree of mutual information (similarity). Within each factor, at least two items shared an amount of I›0.20 mutual information, except for factor 13 (Figure 2). The items within factor 13 displayed no sign of mutual dependence. Those items may have converged in an artificial factor because they had low prevalence rates in common. Thus only factors 1 to 12 and factor 14 were deemed reliable.

ITEM REDUCTION The number of items of the questionnaire was reduced to 52 after the first Delphi round of the expert panel and to 34 items after the second round. In total, 23 items were identified as non-factorable, see Figure 1. Of those, 11 items were retained because of their clinical relevance. Of the 52 factorable items, 28 redundant items were eliminated upon consensus of the expert panel. For example, #33 'My feelings have returned' was considered ambiguous and #11 'My thoughts are calmer' could be substituted by the more specific statement #03 'I can think more clearly'. Similarly, the statements #16 'I think more slowly' and #50 'I move more slowly' were considered redundant to #13 'I react more slowly'. Some of the items were eliminated because they may be stigmatizing or evoke socially desired answers, e.g. #70 'My sex drive is too low'; or because the statement may be dependent on external factors such as the potentially limited social network of inpatients, e.g.#36 'I have more difficulty keeping up with conversations'. After the third Delphi round, consensus was obtained about the 34-item questionnaire (Appendix 1), consisting of 10 desired and 24 undesired experiences with antipsychotics.

INTERNAL CONSISTENCY OF SRA-34 The internal consistency was acceptable for the desired subscale (Cronbach's α=0.82; 9 factorable items), as well as for undesired subscale (α=0.82; 14 factorable items) of the SRA-34.

FIGURE 1. Overview of SRA items eliminated and retained in sequential steps of the analysis.

74	Total number of SRA items
-23	Eliminated non-factorable items (exploratory factor analysis)
12	All loadings ‹0.3
2	Cross-loadings of ›0.30
8	Main factor loading ‹0.50
1	Responded by females only
11	Retained non-factorable items because of clinical relevance (expert panel)
-28	Eliminated factorable items considered redundant (expert panel)
14	ambiguous content
7	non-specific content
4	evoking socially desired responses
3	dependent on external factors
34	Number of items of shorter version of SRA

AD FIGURE 2 (P.97). Similarity matrix, comparing the amount of mutual information shared between all 73 SRA-items (n=1478). All SRA-items on the x- and y-axis were listed according to the factor structure of the exploratory factor analysis. The amount of information shared between two items varied between high (red color) and low (blue color).

TABLE 2. Exploratory factor analysis of the SRA-74, with the prevalence rates for each individual item.Generalized Least Squares factor analysis with Direct Oblimin Rotation identified 14 latent factors. Cross-loadings of item #12 on factor 11 (0.384) and item #27 on factor 3 (0.327) were marked by an asterisk (*). Item #74 was for females only and therefore not included in factor analysis. EPS = Extrapyramidal motor symptoms.

Factor		Items	Factor Loading	Prevalence
1.	Appetite	19. I have an increased appetite	1.098	49%
		32. I am hungry more often	0.689	47%
2.	Slowed Down	16. I think more slowly	0.596	44%
		13. I react more slowly	0.554	52%
		50. I move more slowly	0.431	44%
		26. I can't remember well	0.419	45%
		65. I have more trouble concentrating	0.329	42%
3.	Recovery Cognition	03. I can think more clearly	0.761	77%
		04. I feel calmer	0.711	66%
		02. I am more stable	0.666	63%
		05. I am able to follow conversations better	0.662	78%
		01. I feel more like myself	0.631	79%
		11. My thoughts are calmer	0.537	74%
		12. I feel less confused	*0.414	72%
		35. I have more control over my thoughts	0.304	80%
		30. I am less irritable	‹0.30	85%
4.	Weight Gain	46. I have gained too much weight	-0.958	55%
		60. My weight has increased	-0.898	60%
		66. I am less fit	‹0.30	48%
5.	Recovery Social	63. Dealing with others is easier	-0.871	86%
		61. I dare to make contact with people again	-0.803	86%
		64. I have more interest in my surroundings	-0.709	86%
		71. I am better at holding conversations	-0.603	88%
		62. I feel physically healthier	-0.377	88%
6.	Sexual Problems	70. My sex drive is too low	-0.884	31%
		17. My sex drive has decreased	-0.791	42%
		55. It is more difficult for me to have an orgasm	-0.715	28%
7.	Increased Sleep	10. I sleep too much	0.784	49%
		51. I need more sleep	0.715	62%
		58. I have more difficulty waking up	0.622	48%
		72. I can sleep better	-0.412	71%
		25. I feel more drowsy	0.338	55%
		24. I get mentally tired more quickly	‹0.30	52%

Factor		Items	Factor Loading	Prevalence
8.	EPS	41. My muscles are more tense	0.798	31%
		48. My muscles are more stiff	0.689	36%
		54. I have more tremors	0.385	27%
		56. I have more trouble sitting still	‹0.30	30%
		67. I have a dry mouth more often	‹0.30	36%
9.	Social Withdrawal	68. I have less energy for socializing	0.715	38%
		23. I am less interested in socializing	0.590	34%
		36. I have more difficulty keeping up with conversations	0.475	37%
		37. I am less spontaneous	0.389	38%
		43. I get physically tired more easily	0.330	57%
		73. I am more detached	‹0.30	30%
10.	Flattened Affect	09. My emotions are dull	0.866	54%
		14. My emotions are too dull	0.800	44%
		40. I am less emotional	0.567	42%
		69. My thoughts are subdued	‹0.30	53%
		07. My mind is blank more often	‹0.30	36%
		22. I am less creative	‹0.30	40%
11.	Recovery Psychosis	49. I am less psychotic	0.652	60%
		52. I hear fewer voices	0.458	73%
		18. I am less anxious	0.307	80%
12.	Recovery Attention	28. I am more active	0.594	90%
		29. My memory has improved	0.528	92%
		27. I can concentrate better	*0.471	87%
		34. I feel happier	0.463	89%
		33. My feelings have returned	0.320	93%
		20. I am more confident	‹0.30	84%
		38. My sex drive has increased	‹0.30	9%
13.	Miscellaneous	21. I black-out more often	0.307	20%
		42. I have increased salivation	‹0.30	36%
		44. I am dizzy more often	‹0.30	31%
		57. My vision is more blurred	‹0.30	30%
		59. I am nauseous more often	‹0.30	18%
		45. I am constipated more often	‹0.30	20%
		53. I leak urine more often	‹0.30	20%
		47. I perspire more	‹0.30	33%
14.	Depressive	06. I feel more depressed	-0.584	20%
		15. I feel down	-0.578	33%
		08. I feel more restless	-0.450	23%
		39. I am more irritable	-0.301	20%
		31. I get psychotic symptoms	‹0.30	11%
	Female only	74. I menstruate less often		19%

APPENDIX 1. The SRA-34 questionnaire in random order, divided into nine subscales for undesired effects and five for desired effects. The SRA-34, together with Dutch, French, German, Spanish, Turkish and Arabic translations of the full version, can be downloaded on www.rgoc.nl.

Item	Because of the antipsychotic medication:
01	My emotions are dull
02	I feel happier
03	My weight has increased
04	I have less energy for socializing
05	I can't remember well
06	I react more slowly
07	I am less anxious
08	I feel more depressed
09	I am constipated more often
10	I can concentrate better
11	I leak urine more often
12	My vision is more blurred
13	I have more trouble sitting still
14	I hear fewer voices
15	It is more difficult for me to have an orgasm
16	I have a dry mouth more often
17	My memory has improved
18	I have more tremors
19	I have more interest in my surroundings
20	I am nauseous more often
21	My sex drive has decreased
22	I am dizzy more often
23	Dealing with others is easier
24	I can think more clearly
25	I get physically tired more easily
26	I have more difficulty waking up
27	I am less creative
28	My muscles are more stiff
29	I have more control over my thoughts
30	I have increased salivation
31	I have more trouble concentrating
32	I have an increased appetite
33	I can sleep better
34	I menstruate less often (*for females only*)

Undesired effects

Weight & Appetite (3,32)

Sexual Problems (15,21)

Slowed Down (5,6,31)

EPS (18,28)

Increased Sleep (26)

Social Withdrawal (4,25)

Emotional Flattening (1)

Depressive Symptoms (8)

Other Undesired effects (9,11,12,13,16,20,22,27,30,34)

Desired effects

Recovery Psychosis (7,14)

Recovery Cognition (24,29)

Recovery Social (19,23)

Recovery Attention (2,10,17)

Recovery Increased Sleep (33)

Mutual information I(X, Y)
High
Low
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Item
Factor
1. Appetite
2. Slowed Down
3. Recovery Cognition
4. Weight Gain
5. Recovery Social
6. Sexual Problems
7. Increased Sleep
8. EPS
9. Social Withdrawal
10. Flattened Affect
11. Recovery Psychosis
12. Recovery Attention
13. Misc. Physical
14. Depressive

The SRA-34 is a unique questionnaire to measure a combination of relevant self-reported desired and undesired effects in response to antipsychotic medication. This is the short version of the SRA-74 questionnaire retaining the latent structure by covering 10 desired and 24 undesired effects of antipsychotics. The SRA-34 is internally consistent, having Chronbach's alpha values within the range of the previously reported values for the subscales of the SRA-74.[12] Thus the SRA-34 can be considered a quick and reliable instrument to guide pharmaco-therapeutic treatment in clinical practice.

Exploratory factor analysis of the SRA-74 revealed new symptom dimensions, in addition to the original subscale structure as proposed by Wolters (2006).[12] First, desired effects were divided into four factors (recovery from psychosis, improvement in cognition, attention and social functioning). Second, we identified depressive symptoms as a factor, independent of other emotional experiences. The other factors remained the same (increased sleep, appetite and weight, slowed down behavior, sexual problems, EPS, social withdrawal and flattened affect). Similarity analysis was useful in identifying a number of items that did not belong to any of the factors, such as 'dry mouth' and 'increased salivation'. Of those, experts retained the most clinically relevant items in the SRA-34 according to the Delphi consensus method.

What is the place of the SRA-34 in comparison with existing instruments? The LUNSERS[9] and GASS[10] comprise detailed physical side effects. The SRA-34 not only contains important physical side effects, but also measures psychological effects of antipsychotics, such as emotional, cognitive and social functioning. The SWN well-being questionnaire covers some of the latter psychological effects (e.g. My thinking is difficult and slow), as well as some desired subjective experiences of antipsychotics similar to the SRA-34 (e.g. I find it easy to keep in touch with people around me),[8] but no physical side effects. The SRA-34 can be used for a quick yet comprehensive evaluation of the patients' experiences with antipsychotics. Experiences in response to new medication can be evaluated by assessment of the SRA-34 before and after switching antipsychotics in daily clinical practice or clinical trials. Completing the SRA-34 should take a patient on average 5-10 minutes, about half the time needed to complete the SRA-74.[12] Since we did not change the wording or add new items, we assume that the test-retest reliability of the SRA-34 is comparable to the original version. A next step in the validation of the SRA-34 could be to associate the scores with clinical outcomes, e.g. whether (un)desired effects are predictive for antipsychotic

non-adherence, switching, relapse psychosis or hospitalization.

A strong point of the current study is that our analysis was based on a large sample of patients with psychotic disorders using a wide range of antipsychotics and doses. Our cohort appears to be representative for mental health practice with similar prescribing patterns. An inherent limitation is that patients using co-medication may have difficulties to distinguish antipsychotic effects from effects of other medication, which remains a difficulty and important question for clinicians in daily practice. But because of the large sample size, we believe it unlikely that this introduced systematic bias in our analysis. Another possible limitation of the study was that we applied exploratory factor analysis to a three-point scale (SRA-74), which could lead to an overestimation of the number of factors.[24] We minimized this risk by selecting the Generalized Least Squares method of EFA. Furthermore, the visual representation of the latent structure (by means of similarity analysis based on mutual information) enabled us to detect artificial correlations.

In the clinical situation, the SRA-34 can be used to discuss the balance between desired and undesired of antipsychotics with the patient. In line with previous studies, our patients were rather satisfied with their antipsychotics.[25,26] Asking patients to recall the beneficial effects of antipsychotics (e.g. from treatment-free periods) may support treatment adherence in an indirect manner.[27] Insight in the patients' appraisal of antipsychotics may help the clinician to understand the patients' attitude towards medication and reinforces the process of shared decision making.[28] Monitoring desired and undesired effects could thereby prevent relapse psychosis[29,30] and an increase in costs associated.[31] To conclude, we developed a quick and comprehensive tool to assess desired and undesired effects attributed to antipsychotics, feasible for use in routine clinical practice and clinical trials.

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7

Estimating dopamine D_2 receptor occupancy for doses of eight antipsychotics. A meta-analysis.

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RATIONALE Dose-equivalents based on dopamine D_2 receptor occupancy can be used to compare antipsychotics on D_2 receptor mediated (side) effects such as extrapyramidal symptoms and altered emotional experiences. Previous meta-analyses modeling the dose-occupancy relationship hardly addressed potential heterogeneity of the imaging data.

OBJECTIVES To model the relationship between dose and D_2 receptor occupancy for a series of frequently prescribed antipsychotics, while addressing the potential heterogeneity of the imaging data.

METHODS We conducted a meta-analysis on published D_2 receptor occupancy data (PET and SPECT) in patients with schizophrenia treated with antipsychotics. A non-linear mixed effects model estimated the median D_2 receptor occupancy for a given antipsychotic dose. Heterogeneity between studies was investigated by incorporating study as a random effect in the model, in addition to patient and study specific explanatory variables.

RESULTS Included were 51 studies, describing N=606 patients (mean age 32.2 (±10.8) years; 25.7% female). The models described the dose-occupancy relationship with narrow confidence bands around the therapeutic dose range. Maximum occupancy [95% Confidence Interval] was estimated for haloperidol 91.9% [86.1;97.8], risperidone 92.4% [81.8;100], olanzapine 96.5% [85.8;100], clozapine 61.7% [49.2;74.2], quetiapine 49.1% [18.7;79.6], aripiprazole 86.9% [78.2;95.7], ziprasidone 82.9% [44.9;100] and amisulpride 85.0% [68.5;100]. Inter-individual differences explained most of the variability in occupancy values, besides significant heterogeneity between studies.

CONCLUSIONS Dose-occupancy functions estimated the median level of dopamine D_2 receptor occupancy for eight frequently prescribed antipsychotics in patients with schizophrenia. These dose equivalents can be used to compare antipsychotic effects in epidemiological studies and clinical practice.

Schizophrenia is a chronic psychiatric disease, commonly necessitating lifelong treatment with antipsychotics. Antipsychotic effects are thought to be mainly mediated by blockade of dopamine D_2 receptors, although other receptors may also be important.[1] Imaging studies suggest that effective relief of psychotic symptoms is associated with blockade of at least 65% of striatal D_2 receptors, but some antipsychotics can reach antipsychotic effects below this threshold.[2-4] The latter antipsychotics have weak affinity for the D_2 receptor and dissociate rapidly from the D_2 receptor.[5,6] Such intermittent blockade may avoid continuous or excessive D_2 receptors occupancy (› 80%) and associated side effects such as extrapyramidal symptoms,[7] affective side effects and elevated prolactin levels.[8-10]

Dose equivalents based on D_2 receptor occupancy can be used to compare D_2 receptor mediated (side) effects between antipsychotics and doses. Reliable dose equivalents of D_2 receptor occupancy are difficult to obtain, since most imaging studies describe relatively small samples and use different imaging methods.[11] The interest in meta-analysis and clinical implications of D_2 receptor occupancy data is growing.[10,12-15,16] Yet previous meta-analyses neither investigated the effect of variability between subjects or studies on the variation in estimated occupancy levels, nor reported the level of uncertainty of their estimates (e.g. by confidence intervals).[10,13] Lataster (2010) described the dose-occupancy relationship for three antipsychotics with high affinity for the dopamine receptor, but not for antipsychotics with weak affinity for D_2 receptor (such as amisulpride, clozapine and quetiapine).[10] Another meta-analysis estimated occupancy for some antipsychotics with weak affinity for the dopamine receptor; however these estimates were based on plasma levels and not on dose.[13] Since plasma levels of antipsychotics are infrequently determined in clinical practice, estimates based on antipsychotic dose may be more useful for epidemiological research.

We aim to estimate D_2 receptor occupancy in relation to dose for a series of frequently prescribed antipsychotics, including antipsychotics with weak affinity for the D_2 receptor. The current meta-analysis incorporates the included studies as a random effect to accommodate and investigate heterogeneity between imaging study designs. The resultant functions can serve as dose equivalents to compare the median level of D_2 receptor occupancy between antipsychotics in clinical research of patients with schizophrenia.

DATA COLLECTION A literature search was conducted using the following keywords in the electronic databases PubMed, EMBASE and PsychInfo: 'antipsychotic', 'occupancy' and 'schizophrenia' (a full description of the search terms can be obtained from the author). At first, the authors I.M.L. and K.T. screened titles and abstracts for relevance to the defined topic and, if appropriate, the full paper was examined. References of included articles were checked for other relevant articles.

Inclusion criteria were: (*i*) investigation of D_2 receptor occupancy in striatal areas (including the putamen and basal ganglia), since striatal areas are known to be richer of dopamine-receptors than extrastriatal areas.[17,18] (*ii*) Study populations consisting of patients diagnosed with schizophrenia or psychotic disorders and thereby excluding other diagnostic groups or healthy volunteers as they may have different D_2 receptor densities in the selected brain areas.[19] (*iii*) Patients treated with currently registered antipsychotics.

I.M.L. extracted the level of occupancy corresponding to antipsychotic dose from the selected papers. Patient characteristics and methodological aspects were recorded as well. If needed, depot dosages were converted to daily doses. Imaging technique was coded into a binary variable indicating Positron Emission Tomography (PET) or Single-Photon Emission Computed Tomography (SPECT). If only average values were presented or the data was presented in a graph, the authors were contacted to retrieve individual data points. Only those antipsychotics with data-points available for the whole therapeutic window were selected for the non-linear regression analysis.

STATISTICAL ANALYSIS

OUTLINE All statistical analyses were conducted with Statistical Analysis Software (SAS), version 9.2 and 9.3. Data were summarized using descriptive measures to describe the population of patients. Furthermore, a mixed-effects non-linear regression analysis was applied to describe the relationship between antipsychotic dose and D_2 receptor occupancy for each antipsychotic separately. This relationship was described by a Michaelis Menten curve, in line with previous imaging studies.[20,21] In addition to previous meta-analyses,[10,13] possible heterogeneity between studies as well as inter-individual variation within studies were modeled as random effects. To explain the variability, we investigated the effect of study specific and patient specific

variables on the D_2 receptor occupancy. The parameters in the non-linear mixed models were estimated with maximum likelihood using the procedure NLMIXED of SAS. More specific details on the statistical analysis are found hereafter.

TRANSFORMATION OF OCCUPANCY D_2 receptor occupancy is the inhibition of binding potential by the antipsychotic in a patient compared to an untreated reference group (baseline). D_2 receptor occupancy (O_{ij}) can be calculated by the formula

(3.1) $$O_{ij} = \frac{BP_i^R - BP_{ij}^P}{BP_i^R}$$

with BP_{ij}^P the binding potential of a patient j in study i and BP_i^R the average binding potential of a reference group. A reference group consisting of untreated subjects is used to estimate the level of baseline occupancy for patients in untreated condition. The resultant fraction was used in our analysis, but the fraction is usually multiplied by 100% to express occupancy as a percentage. Occupancy values of 100% or higher were considered theoretically impossible as this would indicate a negative binding potential in a patient, and were therefore omitted from the statistical analysis. Negative occupancy values may be related to the use of an independent reference group and were maintained in the statistical analysis.

In meta-analysis, the reference groups typically differ across studies, hence their effect should be regarded random as opposed to fixed when a single study is investigated.[22] By logarithmic transformation of our data, we were able to separate the variability between patients and between studies in an additive way, i.e. .

$$Z_{ij} = \log(1 - O_{ij}) = \log(BP_{ij}^P) - \log(BP_i^R)$$

NON-LINEAR MIXED EFFECTS MODEL The transformed occupancy Z_{ij} can be described in a more general form as,

(3.2) $$Z_{ij} = \eta_\theta(x_{ij}) + \sum \beta_k u_{kij} + \gamma_i + \varepsilon_{ij}$$

where $\eta_\theta(x)$ determines the relationship between dose x and D_2 receptor occupancy. The dose-response relationship is a Michaelis-Menten curve of the form $O_{D_2}(x) = \theta_1 x / (\theta_2 + x)$, with dose $x \geq 0$, $\theta_1 \in [0 ; 1]$ the maximal occupancy for the population (E_{max}) and $\theta_2 > 0$, the dose that is associated with 50% reduction in binding potential (EC_{50}).[20,21] In case this dose-response relationship includes a shape parameter q_3

(the Hill coefficient), the hyperbolic function arises $O_{D_2}(x) = \theta_1 x^{\theta_3} / (\theta_2^{\theta_3} + x^{\theta_3})$.[22,21] The shape parameter θ_3 is often assumed to be equal to one, which reduces the hyperbolic function to a Michaelis-Menten curve.[23] For our meta-analysis, the same logarithmic transformation as described for the occupancy values was applied to this hyperbolic function $O_{D_2}(x)$ to get $\eta_\theta(x)$ in (3.2), i.e. $\eta_\theta(x) = \log(1 - O_{D_2}(x))$. The transformed occupancy Z_{ij} in (3.2) may also depend on study specific variables (such as imaging technique) and patient specific variables (such as age and gender). These variables are represented by $u_{0ij}=1$, u_{1ij}, u_{2jk}, ..., u_{mjk} in (3.2) and their fixed effects are determined by the parameters β_0, β_1, ..., β_m. The model parameter γ_i represents the additive random effect of unexplained inter-study variation (heterogeneity between studies) and ε_{ij} represents the unexplained intra-study (inter-individual) variation. These random effects are assumed to be mutually independently and normally distributed with zero mean and their variances are indicated by σ_S^2 and σ_P^2, respectively. For more information on non-linear mixed effects models, see Vonesh and Chinchilli (1997).[24]

PERFORMANCE MEASURES The total variation in observed occupancy values was given by the relative standard deviation (RSD).[25] The RSD can be expressed as a percentage and it is calculated by $100\% \cdot \sqrt{\exp\{\sigma_S^2 + \sigma_P^2\} - 1}$. Heterogeneity between studies was compared to the total variation by means of an intraclass correlation coefficient (ICC), i.e. $100\% \cdot \sigma_S^2 / (\sigma_S^2 + \sigma_P^2)$. This is an important measure for meta-analysis, since an ICC value quantifies the amount of heterogeneity between studies. If the ICC value is zero, there is no heterogeneity between studies and all variability in occupancy values is determined by inter-individual differences. The variances σ_S^2 and σ_P^2 can be derived from model (3.2) and used to estimate the RSD(%) and ICC(%).

Finally, an R^2-value was calculated to evaluate how well the non-linear mixed model predicted the occupancy values. The best linear unbiased predictions (BLUP's) for model (3.2) were determined first with the empirical Bayes estimator and then the R^2 was calculated using a linear regression analysis on the log transformed occupancies with the predictions as explanatory variable.

MODEL BUILDING Model fitting started with the assumption that the dose-response relationship for the median occupancy was of the form of Michaelis-Menten (i.e. $\theta_3 = 1$). The second assumption was that heterogeneity between studies did not exist

($\sigma_G = 0$), since the binding potentials should be normalized with appropriate reference groups. Thirdly, all three explanatory variables age, gender and imaging method were included in the model, but an intercept was omitted from the model since the explanatory variables were centralized with their means. If the reference groups used in the studies are representative for patients, the intercept (constant) β_0 should be equal to $\beta_0 = -\sum \beta_k \bar{u}_{k\cdot\cdot}$, with $\bar{u}_{k\cdot\cdot}$ the average value of explanatory variable k. Thus the centralized variables result in an intercept equal to zero. Note that if the administered dose (x) would be equal to zero, $\eta_\theta(x)$ becomes zero as well.

Heterogeneity between studies was investigated using the likelihood ratio test. If heterogeneity was significant at the level of $\alpha = 0.05$, a random effect for study (γ_i) was included in the model. The contribution of the three explanatory variables was investigated by conducting a backward elimination on the basis of the P-value of these variables for the Wald statistic. Explanatory variables remained in the model if the largest P-value of the variables was below the significance level of $\alpha = 0.05$.

The obtained model was further investigated for goodness-of-fit using the likelihood ratio test. Firstly, the assumption that no bias was present in baseline binding potential of patients with respect to the reference group was verified by evaluating the contribution of an intercept to model (3.2). Secondly, the assumption that the shape parameter θ_3 was equal to one was investigated. An observed lack-of-fit was corrected by including an intercept and/or changing the value of the shape parameter.

The final non-linear model was transformed back to obtain predictions of the median D_2 receptor occupancy values ($\hat{O}_{D_2}$) at different doses. The predictions and the observed occupancy values were graphically displayed together with their confidence intervals. The confidence intervals on the predicted occupancy values, the model parameters, the relative standard deviation, and the intra-class coefficient were constructed using the delta method.[26,27]

The literature search retrieved a total of 50 studies, reporting occupancy data of N=606 patients, divided over 74 treatment arms for 8 antipsychotics (Supplemental Figure 1; Supplemental Table 1). For 86% complete information on age and gender was available, with a mean age of 32.2 (±10.8) years and 25.7% being female (Supplemental Table 2). For amisulpride, age and gender were available for less than 50% of the cases. Other information was reported inconsistently (e.g. the time of scanning after the last antipsychotic dose was known for only 57% of the cases) and was therefore not considered in the statistical analysis.

Fitting model (3.2) including the explanatory variables (age, gender, imaging method; if present for more than 50%) showed that heterogeneity between studies was significant for haloperidol ($P < 0.001$), risperidone ($P < 0.001$), olanzapine ($P < 0.001$), clozapine ($P = 0.036$) and amisulpride ($P = 0.006$) but not for quetiapine ($P = 0.500$). For aripiprazole only one study was available and for ziprasidone the imaging technique confounded the two studies. None of the three explanatory variables significantly contributed to the non-linear models at the level of $\alpha = 0.05$.

The 95% confidence intervals of the estimated maximum occupancy in Table 1 suggest that 100% occupancy was not reached by haloperidol, clozapine, quetiapine and aripiprazole. The total relative standard deviation (RSD) was high for all antipsychotics, especially for haloperidol and risperidone. The high ICC value for haloperidol demonstrated that the variance in occupancy was predominantly explained by heterogeneity between studies, whereas for risperidone and other antipsychotics the variance was dominated by inter-individual variation. The R^2 values also demonstrated substantial variability around the estimated curves. Only haloperidol had an acceptable R^2 value (72.4%) for prediction of individual occupancy values, when correcting for heterogeneity between studies.

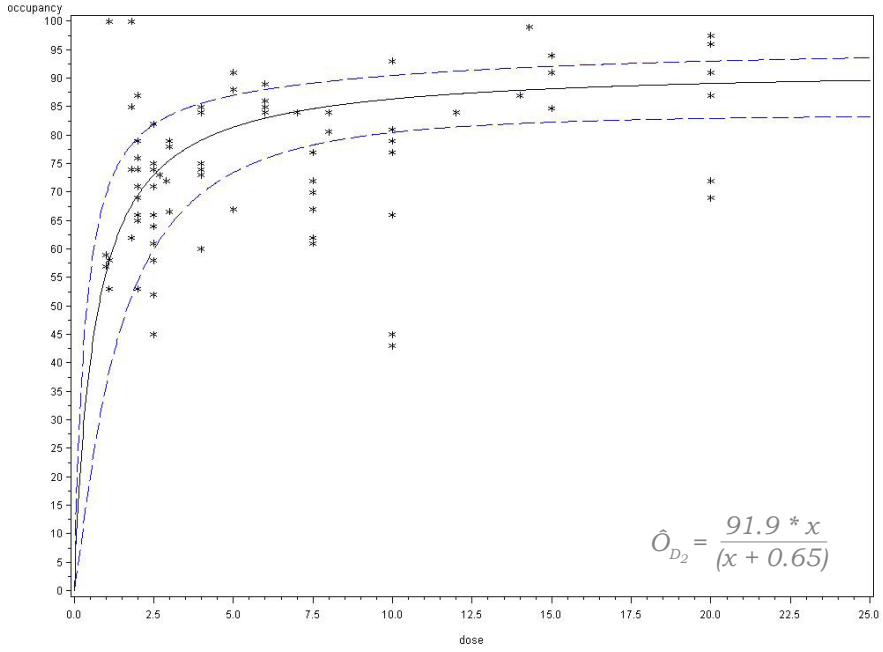
The goodness-of-fit investigation demonstrated no significant bias in the median occupancy by baseline binding potential of the reference groups for any antipsychotic; the lowest two P-values were obtained for olanzapine ($P = 0.051$) and quetiapine ($P = 0.187$). Furthermore, goodness-of-fit could not demonstrate a shape parameter unequal to one for any of the proposed Michaelis-Menten curves; with the lowest p-value obtained for quetiapine ($P = 0.180$). Agent-specific hyperbolic functions of estimated D_2 receptor occupancy $(\hat{O}_{D_2})$ with their 95% confidence intervals are presented in Figure 1.

TABLE 1. Agent-specific estimates of the maximal occupancy E_{max} (θ_1) and concentration associated with 50% reduction in binding potential EC_{50} (θ_2) and 95% confidence intervals. The median level of D_2 receptor occupancy $(\hat{O}_{D_2})$ can be estimated by entering antipsychotic dose (x) in the Michaelis-Menten function $(\hat{O}_{D_2})(x) = E_{max} * x/(x + EC_{50})$. Total RSD = relative standard deviation; ICC = intraclass correlation coefficient, representing heterogeneity between studies a percentage of the total variation; R^2 = percentage of variability in the data explained by the non-linear mixed effects model.

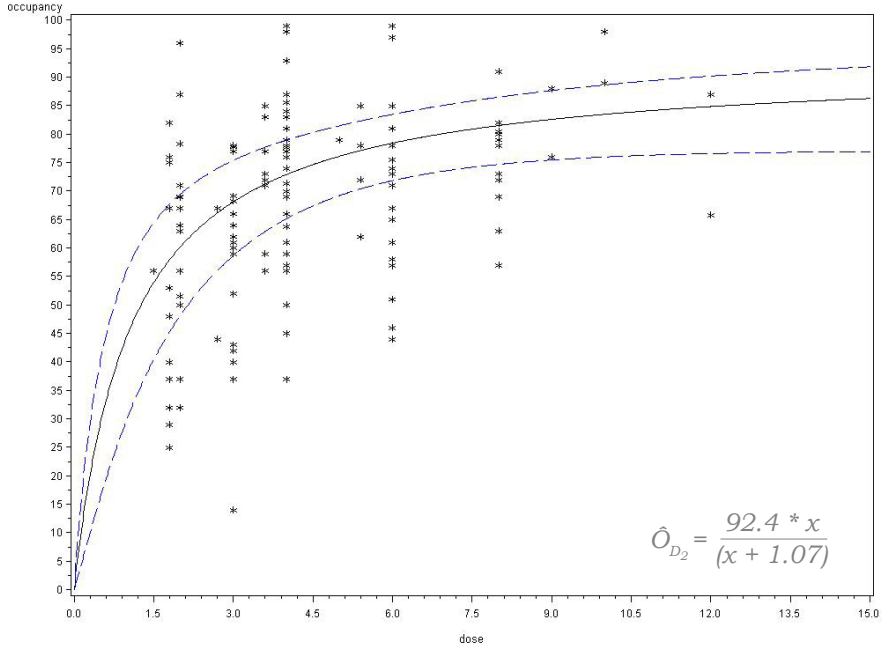
Antipsychotic	E_{max} (θ_1)		EC_{50} (θ_2)		Total RSD (%)		ICC (%)		R^2 (%)
Haloperidol	91.9	[86.1 ; 97.8]	0.65	[0.12 ; 1.18]	81.2	[48.2 ; 114]	67.9	[44.9 ; 91.0]	72.4
Risperidone	92.4	[81.8 ; 100]	1.07	[0.30 ; 1.84]	79.7	[62.7 ; 96.8]	26.8	[4.8 ; 48.8]	41.1
Olanzapine	96.5	[85.8 ; 100]	6.46	[2.46 ; 10.5]	52.7	[39.8 ; 65.6]	31.6	[2.5 ; 60.7]	56.7
Clozapine	61.7	[49.2 ; 74.2]	125	[19.8 ; 230]	28.9	[24.3 ; 33.5]	14.2	[0 ; 34.9]	31.1
Quetiapine	49.1	[18.7 ; 79.6]	352	[0 ; 921]	29.4	[23.6 ; 35.1]	0	NA	33.1
Aripiprazole	86.9	[78.2 ; 95.7]	0.25	[0 ; 1.71]	58.8	[33.3 ; 84.2]	0	NA	1.0
Ziprasidone	82.9	[44.9 ; 100]	41.7	[0 ; 119]	42.5	[29.1 ; 55.9]	0	NA	8.9
Amisulpride	85.0	[68.5 ; 100]	137	[0 ; 313]	51.6	[26.6 ; 76.5]	39.7	[0 ; 91.0]	64.3

AD FIGURE 1 (P.112-115). Individual occupancies and Michaelis-Menten curves describing dopamine D_2 receptor occupancy for: A) haloperidol, B) risperidone, C) olanzapine, D) clozapine, E) quetiapine, F) aripiprazole, G) ziprasidone, H) amisulpride. The median D_2 receptor occupancy $(\hat{O}_{D_2})$ can be estimated by entering antipsychotic dose (x) in the function $(\hat{O}_{D_2})(x) = E_{max} * x/(x + EC_{50})$, see also Table 1.

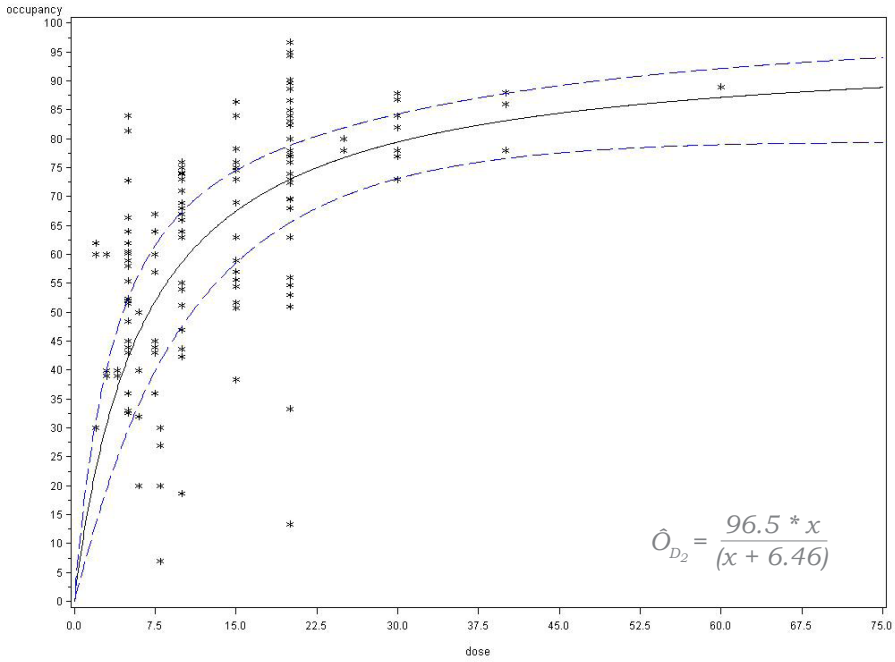
1A. HALOPERIDOL INDIVIDUAL AND MEDIAN OCCUPANCY



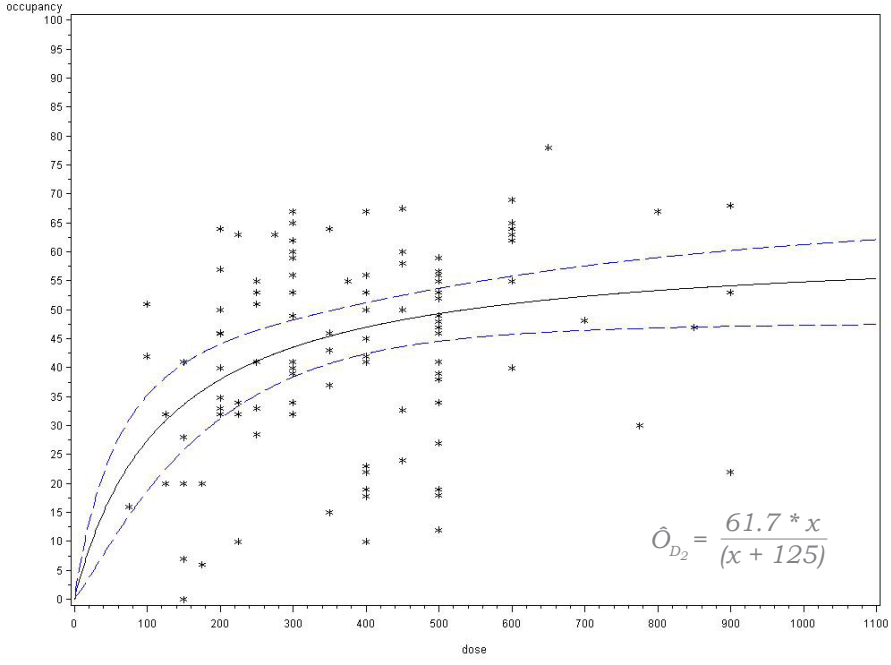
1B. RISPERIDONE INDIVIDUAL AND MEDIAN OCCUPANCY



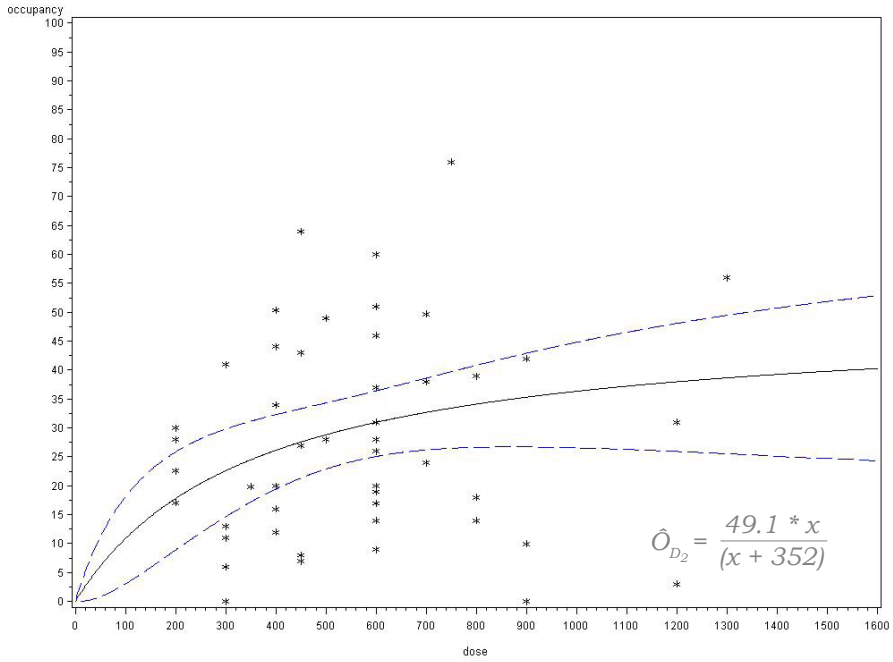
1C OLANZAPINE INDIVIDUAL AND MEDIAN OCCUPANCY



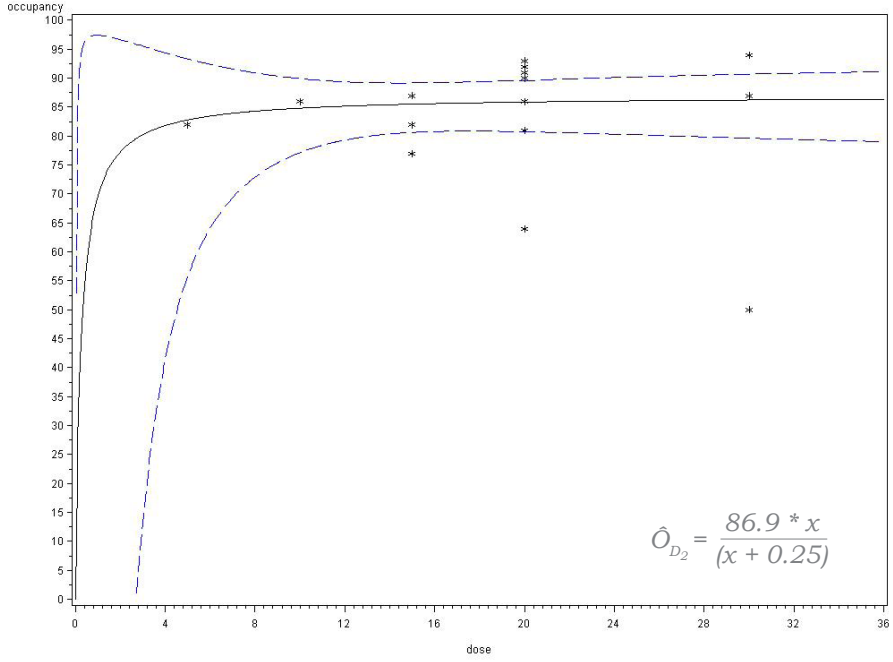
1D CLOZAPINE INDIVIDUAL AND MEDIAN OCCUPANCY



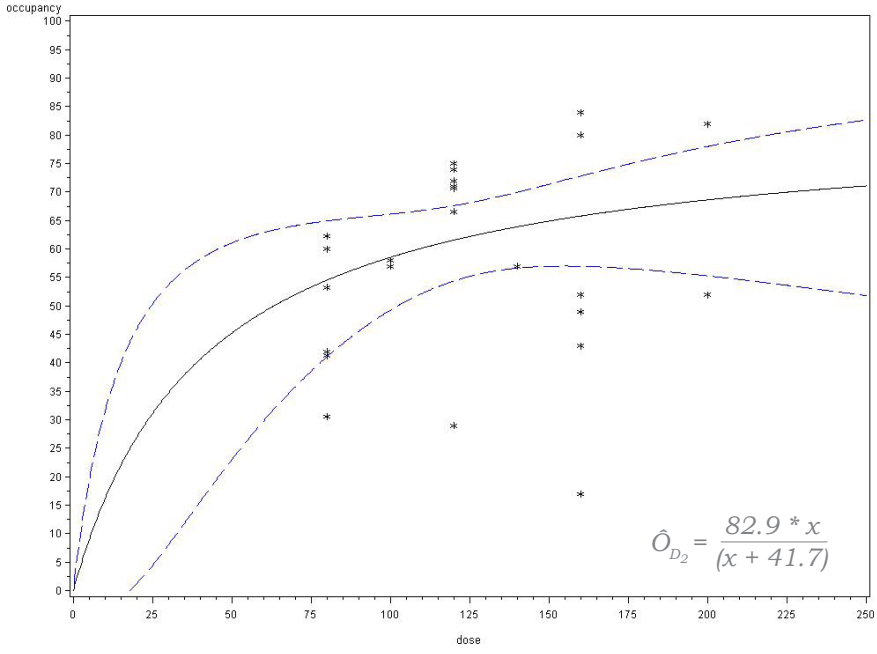
1E QUETIAPINE INDIVIDUAL AND MEDIAN OCCUPANCY



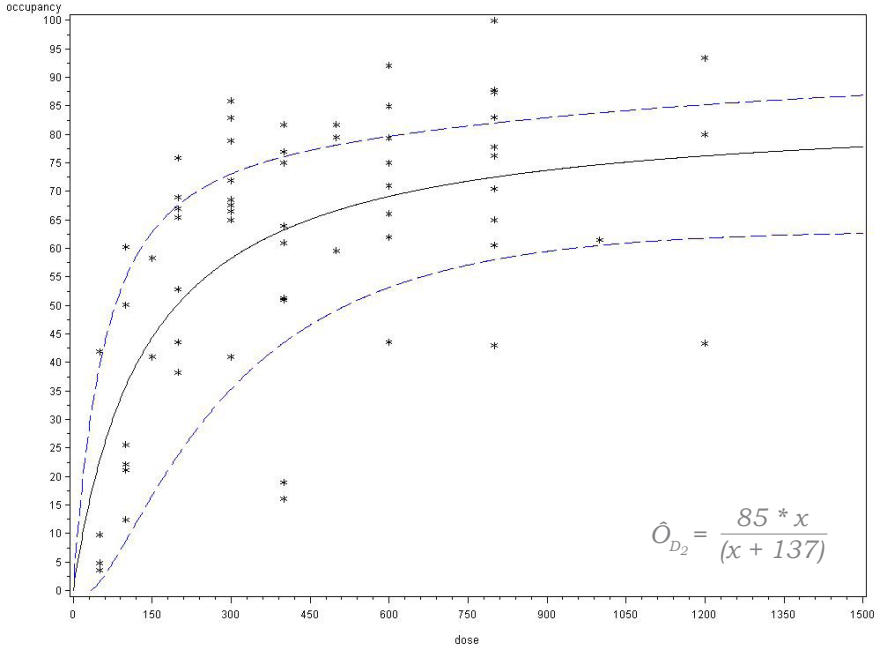
1F ARIPIPRAZOLE INDIVIDUAL AND MEDIAN OCCUPANCY



1G ZIPRASIDONE INDIVIDUAL AND MEDIAN OCCUPANCY



1H AMISULPRIDE INDIVIDUAL AND MEDIAN OCCUPANCY



This meta-analysis provided eight functions to estimate the level of D_2 receptor occupancy for a given antipsychotic dose in patients with psychotic disorders. The dose-occupancy relationships of quetiapine and aripiprazole have not been modeled by previous meta-analyses. Our dose-occupancy functions can be used in epidemiological and clinical studies to compare D_2 receptor mediated (side) effects between antipsychotics and doses. For example to optimize treatment strategies by finding thresholds of D_2 receptor occupancy indicative for D_2 receptor mediated (side) effects.[14,28,29] This means that our functions can be used as an alternative to the conventional methods to determine equivalent doses of different antipsychotics, such as the defined daily dose (DDD),[30] haloperidol or chlorpromazine equivalents.[31,32] Dose-occupancy equivalents may have more face validity with respect to D_2 receptor mediated (side) effects than the conventional equivalents, which rely on the clinical effectiveness of comparable antipsychotic doses.

The dose-occupancy functions reflected the pharmacodynamic properties of the antipsychotics.[5] The maximal D_2 receptor occupancy was high for strong dopamine antagonists (E_{max} › 90%; haloperidol and risperidone) and could easily be distinguished from low maximal occupancy of weak dopamine antagonists like clozapine and quetiapine (E_{max} ‹ 65%). Strong dopamine antagonists had steep curves in the therapeutic dose window in combination with large inter-individual variation in D_2 occupancy. Hence it is challenging to determine which doses are associated with threshold occupancy values indicative for D_2 receptor mediated side effects.[33,34,35] Threshold values for these antipsychotics should be reported as ranges rather than absolute values.[3] Alternatively, the weak dopamine antagonists had low maximal occupancy values and relatively little variability in occupancy values, suggesting that high doses of those antipsychotics are not likely to exceed thresholds of ›80% occupancy, indicative for D_2 receptor mediated side effects.[35]

A comparison of our dose-occupancy models with previous literature is restricted to one meta-analysis of three antipsychotics.[10] Lataster (2010) restrained the maximum level of striatal D_2 receptor occupancy by infinite antipsychotic doses to 100%,[10] while our estimates of maximal occupancy of the D_2 receptors varied between 49-96% occupancy. Their 'restrained' model might not hold for haloperidol, as the maximum level of 100% occupancy was not within our confidence limits for haloperidol. Especially when modeling antipsychotics with high affinity for the D_2 receptor, deviations from the estimated median occupancy should not exceed 100% occupancy (as these

values could be interpreted as theoretically impossible negative binding potentials). A recent meta-analysis based on plasma levels also demonstrated that models with an estimated maximal occupancy outperformed restrained models with a maximal occupancy set at 100%.[13] Most of the estimates of maximal occupancy by Uchida (2011) were within our confidence limits, although their estimates based on plasma levels were slightly lower than our estimates based on dose.[13] These relatively minor differences may be related to their selective inclusion of SPECT studies providing plasma levels and differences in dealing with the data. The comparison with previous meta-analyses suggested that our models provided the most reliable estimates of D_2 receptor occupancy in patients with schizophrenia, when using antipsychotic dose as predictor. The low R^2 values of our study suggested that that occupancy values are difficult to predict for individual patients, but the narrow confidence bands around the therapeutic window of the curves indicated that the median occupancy was precisely estimated. Note that the RSD and ICC values implied that the R^2 value of haloperidol may be inflated due to heterogeneity between studies.

The current meta-analysis was the first to quantify the differences in occupancy values between studies (heterogeneity). The intraclass correlation coefficient (ICC) demonstrated that inter-individual differences dominated the variability in occupancy values for most antipsychotics. Of note, the inter-individual differences could not be explained by age or gender, in line with previous literature.[36] A considerable amount of variability was explained by heterogeneity between studies, especially for haloperidol. The observed heterogeneity between studies may reflect variation in methodology, such as the brain imaging technique.[11] In contrast to the previously reported reduction of occupancy by SPECT compared to PET,[37] our meta-analysis could not attribute the observed heterogeneity to the imaging technique. Other study characteristics possibly contributing to the variation in baseline occupancy values between studies could be the choice of the reference region,[37] radioligand,[38,39] or the composition of the reference group to correct for inter-individual variation in dopamine D_2 receptor density.[36,40] Methodological aspects that may alter the shape of the dose-response relationship, could be the route of administration (oral/depot), the use of concomitant medication or the time of measurement after last antipsychotic dose.[41] Future research of study characteristics affecting the variability in occupancy could lead to more standardized methodology in imaging studies. Furthermore, investigating the contribution of patient characteristics such as metabolism or genetic background to D_2 receptor occupancy would help to understand the large inter-individual differences.[42] This would most

likely also improve the predictability of our curves for individual patients.

One of the limitations of the current study was a lack of experimental data outside the therapeutic dose-range of aripiprazole and ziprasidone, which was reflected by low R^2 values and wide confidence bands around the lower and upper ends of the curves. We would therefore recommend applying the functions of aripiprazole and ziprasidone to patients with doses within the therapeutic dose range (aripiprazole: 10–30 mg/day; ziprasidone: 80–200 mg/day).[43] Patients participating in the imaging studies included in this meta-analysis were relatively young (mean age: 32 years), so it is unknown whether our findings can be extrapolated to elderly patients. Dose-occupancy functions for the D_2 receptor alone cannot serve to determine the therapeutic window of antipsychotics, as therapeutic effect may not only be dependent on D_2 receptor blockade seen the multi-receptor affinity of most antipsychotics (e.g. serotonin 5-HT receptor).[44]

In summary, we provided precise estimates of the median level of dopamine D_2 receptor occupancy for eight frequently prescribed antipsychotics, using improved statistical methods for meta-analyses of published imaging data. Our dose-occupancy functions can be applied in epidemiological and clinical studies investigating D_2 receptor mediated (side) effects in absence of *in vivo* occupancy measures of patients with psychotic disorders.

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SUPPLEMENTAL TABLE 1. Studies included for review. PET = Positron Emission Tomography; SPECT = Single-Photon Emission Computed Tomography

	Study	Radioligand	Antipsychotic	Route	Patients
1	Bigliani et al. (2000) [1]	[^{123}I] epipride SPET	olanzapine	oral	5
2	Bressan et al. (2003a) [2]	[^{123}I] epipride SPET	amisulpride	oral	8
3	Bressan et al. (2003b) [3]	[^{123}I] epipride SPET	risperidone	oral	6
4	Catafau et al. (2009) [4]	[^{11}C] raclopride PET	clozapine	oral	8
			olanzapine	oral	5
			risperidone	oral	7
5	Coppens et al. (1991) [5]	[^{11}C] N-methyl-spiperone PET	haloperidol	oral	2
6	Corripio et al. (2005) [6]	[^{123}I] IBZM-SPECT	ziprazidone	oral	10
7	de Haan et al. (2003) [7]	[^{123}I] IBZM-SPECT	haloperidol	oral	11
			olanzapine	oral	9
8	Dresel et al. (1999) [8]	[^{123}I] IBZM-SPECT	olanzapine	oral	20
9	Farde et al. (1989) [9]	[^{11}C] raclopride PET	clozapine	oral	2
10	Farde and Nordstrom (1992) [10]	[^{11}C] raclopride PET	clozapine	oral	5
			haloperidol	oral	8
11	Farde et al. (1994) [11]	[^{11}C] raclopride PET	clozapine	oral	16
12	Farde et al. (1997) [12]	[^{11}C] raclopride PET	clozapine	oral	1
			haloperidol	depot	2
13	Gefvert et al. (2005) [13]	[^{11}C] raclopride PET	risperidone	depot	8
14	Goyer et al. (1996) [14]	[^{11}C] raclopride PET	clozapine	oral	5
			haloperidol	oral	2
15	Grunder et al. (2006) [15]	[^{18}F] fallypride PET	clozapine	oral	15
16	Grunder et al. (2008) [16]	[^{18}F] fallypride PET	aripiprazole	oral	16
17	Kapur et al. (1996) [17]	[^{11}C] raclopride PET	haloperidol	oral	7
18	Kapur et al. (1997) [18]	[^{11}C] raclopride PET	haloperidol	oral	6
19	Kapur et al. (1999) [19]	[^{11}C] raclopride PET	clozapine	oral	11
			olanzapine	oral	17
			risperidone	oral	16
20	Kapur et al. (2000) [20]	[^{11}C] raclopride PET	quetiapine	oral	14
21	Kapur et al. (2001) [21]	[^{11}C] raclopride PET	clozapine	oral	5
22	Kessler et al. (2006) [22]	[^{11}C] raclopride PET	clozapine	oral	6
		[^{18}F] fallypride PET	quetiapine	oral	7
23	Knable et al. (1997) [23]	[^{123}I] IBZM-SPECT	haloperidol	oral	7
			risperidone	oral	12
24	Kufferle et al. (1996) [24]	[^{123}I] IBZM-SPECT	risperidone	oral	11
25	Kufferle et al. (1997) [25]	[^{123}I] IBZM-SPECT	clozapine	oral	6
			haloperidol	oral	8

	Study reference	Imaging technique	Antipsychotic	Route	Patients
			quetiapine	oral	4
26	Kunstler et al. (2000) [26]	[123I] IBZM-SPECT	clozapine	oral	4
			haloperidol	depot	12
			risperidone	oral	7
27	la Fougere et al. (2005) [27]	[123I] IBZM-SPECT	amisulpride	oral	29
28	Lavalaye et al. (1999) [28]	[123I] IBZM-SPECT	olanzapine	oral	22
			risperidone	oral	13
29	Martinot et al. (1996) [29]	[76BR] FLB 457 PET	amisulpride	oral	11
30	Meisenzahl et al. (2000) [30]	[123I] IBZM-SPECT	olanzapine	oral	20
31	Nikisch et al. (2010) [31]	[18F] fallypride PET	quetiapine	oral	5
32	Nordstrom et al. (1993) [32]	[11C] raclopride PET	clozapine	oral	2
33	Nordstrom et al. (1995) [33]	[11C] N-methyl-spiperone PET	haloperidol	oral	6
34	Nordstrom et al. (1998) [34]	[11C] raclopride PET	olanzapine	oral	3
35	Pickar et al. (1996) [35]	[123I] IBZM-SPECT	clozapine	oral	7
36	Raedler et al. (1999) [36]	[123I] IBZM-SPECT	olanzapine	oral	10
37	Regenthal et al. (2005) [37]	[123I] IBZM-SPECT	risperidone	oral	8
38	Remington et al. (2006) [38]	[11C] raclopride PET	risperidone	depot	9
39	Schmitt et al. (2002) [39]	[123I] IBZM-SPECT	risperidone	oral	20
40	Stephenson et al. (2000) [40]	[123I] epipride SPET	quetiapine	oral	6
41	Talvik et al. (2001) [41]	[11C] raclopride PET	clozapine	oral	4
			haloperidol	oral	3
42	Tauscher et al. (1997) [42]	[123I] IBZM-SPECT	haloperidol	oral	1
			quetiapine	oral	1
43	Tauscher et al. (1999) [43]	[123I] IBZM-SPECT	clozapine	oral	6
			haloperidol	oral	10
			olanzapine	oral	6
44	Uchida et al. (2008) [44]	[11C] raclopride PET	risperidone	depot	7
45	Uchida et al. (2009) [45]	[11C] raclopride PET	risperidone	oral	4
46	Vernaleken et al. (2004) [46]	[18F] fallypride PET	amisulpride	oral	9
47	Vernaleken et al. (2008) [47]	[18F] fallypride PET	ziprazidone	oral	15
48	Vernaleken et al. (2010) [48]	[18F] fallypride PET	quetiapine	oral	16
49	Vesely et al. (2000) [49]	[123I] IBZM-SPECT	quetiapine	oral	2
50	Wiesel et al. (1990) [50]	[11C] raclopride PET	haloperidol	oral	1
51	Xiberas et al. (2001) [51]	[76BR] FLB 457 PET	amisulpride	oral	5
			clozapine	oral	3
			haloperidol	oral	4
			olanzapine	oral	4
			risperidone	oral	3

SUPPLEMENTAL TABLE 2. Overview of the number studies, used imaging techniques and patient characteristics for each antipsychotic. PET = Positron Emission Tomography; SPECT = Single-Photon Emission Computed Tomography

	Studies (N)		Patients (N)		Age	Gender	Dose	Occupancy
Antipsychotic	PET	SPECT	PET	SPECT	(mean years)	(% female)	(mean mg/day)	(mean %)
Haloperidol	10	6	41	49	29.9	40.7	6.78	75.7
Risperidone	7	8	47	84	33.8	28.3	4.40	67.9
Olanzapine	4	8	24	97	30.9	30.9	13.8	61.5
Clozapine	13	5	75	31	33.8	31.7	384	43.0
Quetiapine	4	4	42	13	34.4	20.0	542	25.0
Aripiprazole	1	-	16	0	30.3	0.0	18.8	83.0
Ziprasidone	1	1	15	10	30.5	26.7	126	58.0
Amisulpride	3	2	25	37	29.6	18.2	447	59.9

SUPPLEMENTAL FIGURE 1. Search results on dopamine D_2 receptor occupancy. A combination of the following search terms were entered in electronic databases Pubmed, Embase and PsychINFO in March 2011: occupancy, imaging, dopamine D_2 receptor, schizophrenia, antipsychotic.

Total number of references:	1682	
Duplicates		540
Unique references screened on title/abstract	1142	
Excluded on title/abstract		1002
No striatal D_2 receptor occupancy measured		311
No (registrated) antipsychotics		113
No schizophrenia patients (healthy subjects/in vivo/vitro)		276
No original report: review / comment		292
Dissertation/conference abstract		8
Other language than En,Fr,Ger,Dutch		2
Included for full-text review	140	
Excluded after full-text review		89
No striatal D_2 receptor occupancy measured		6
No (registrated) antipsychotics		10
No schizophrenia patients (healthy subjects/in vivo/vitro)		5
No individual datapoints (in graph, ratio or mean values)		56
Data represented elsewhere (preliminary sample/repetition)		12
Publications selected for analysis	51	

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8

Dopamine D_2 receptor involvement in altered emotional experiences attributed to antipsychotic medication

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BACKGROUND Altered emotional experiences in response to antipsychotics may increase the burden of disease in patients with schizophrenia. We studied the association between altered emotional experiences and D_2 receptor affinity and occupancy for six frequently prescribed antipsychotics.

METHODS In a cross-sectional study, patients with schizophrenia completed the Subjects Reaction to Antipsychotics questionnaire to assess whether they attributed altered emotional experiences, operationalized as flattened affect or depressive symptoms, to their antipsychotics. The association between altered emotional experiences, antipsychotic D_2 receptor affinity (categorized as high for haloperidol and risperidone, medium for olanzapine, weak for clozapine and quetiapine, and partial for aripiprazole) and the estimated level of D_2 receptor occupancy, based on the patients' antipsychotic daily dose, was quantified using logistic regression analysis. By logistic regression analysis we also compared the risk of altered emotional experiences between patients using antipsychotic monotherapy and combination therapy.

RESULTS Of the 1298 included patients, 302 (23%) reported flattened affect and 212 (16%) depressive symptoms in response to their antipsychotic treatment. Altered emotional experiences were neither related to antipsychotic D_2 receptor affinity, nor to D_2 occupancy, nor to an interaction between the two in patients using antipsychotic monotherapy. Patients using antipsychotic combination therapy (n=288; 22%) were more likely to attribute depressive symptoms to their antipsychotics than patients using antipsychotic monotherapy (OR[95%CI] = 1.443[1.033 – 2.015]).

DISCUSSION Altered emotional experiences were not related to the level of D_2 receptor affinity or occupancy in patients on antipsychotic monotherapy. The risk of depressive symptoms was increased in patients on combination therapy.

Patients with schizophrenia may experience altered emotions in response to antipsychotic treatment,[1-3] also known as neuroleptic dysphoria. Altered emotional experiences include depressive symptoms, flattened emotions or inability to experience pleasure (anhedonia). They further increase the burden of disease and lead to non-adherence with antipsychotic medication.[4,5]

Antipsychotics exert at least part of their therapeutic effect by blockade of striatal dopamine receptors.[6] Animal research has shown that chronic blockade of dopamine D_2 receptors in the mesolimbic brain areas disturb the reward system, which may lead to relative anhedonia.[7,8] A dose-dependent relationship with altered emotional experiences has been demonstrated for first generation antipsychotics in patients with schizophrenia.[9,10] Imaging studies found an association between altered emotional experiences and increased levels of D_2 receptor occupancy.[11-14] Lataster (2011) found a significant interaction effect between high D_2 receptor occupancy and haloperidol, but not risperidone or olanzapine, on emotional experiences.[15] These findings implied that antipsychotics with high affinity for the D_2 receptor are most likely to be associated with altered emotional experiences. So far, studies reporting such associations found minimal effect sizes and included small study groups without a control group using antipsychotics with medium or weak affinity for the D_2 receptor.[12,14,15] It remains unknown whether antipsychotics with weak affinity for (or rapid dissociation from) the D_2 receptor have a decreased risk to alter emotional experiences compared to antipsychotics with high the D_2 receptor affinity.[16,17] The antagonistic effects of some antipsychotics on the serotonin 5-HT_{2a} receptor, has also been proposed to mediate a reduction of depressive symptoms, possibly interacting with depressogenic effects of dopamine blockade.[18]

The current study investigated the effects of antipsychotics on emotional experiences in a large cross-sectional sample of patients with psychotic disorders using six frequently prescribed antipsychotics with distinct D_2 receptor affinities. We studied the association between altered emotional experiences and antipsychotic affinity for the D_2 receptor, an estimated level of D_2 receptor occupancy, or an interaction between the two using logistic regression analysis.

SUBJECTS A cross-sectional study was conducted in a population of adult patients with schizophrenia or related psychotic disorders receiving mental health care in the North of the Netherlands, who participated in the annual screening program Pharmacotherapy Monitoring and Outcome Study (PHAMOUS).[19,20] The investigation was carried out between January 2007 and April 2010 and was in accordance with the latest version of the Declaration of Helsinki. Altered emotional experiences in response to antipsychotics were assessed by the Subjects Reaction to Antipsychotics (SRA), a self-report questionnaire designed to measure desired and undesired effects of antipsychotics.[21] The SRA was sent out by mail prior to the PHAMOUS screening. Patients having difficulties filling out the questionnaires due to concentration problems or cognitive impairment received help from the nurse during the screening.

A psychiatrist diagnosed each patient according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) classification system.[22] The patient's psychiatrist or case manager rated the quality of mental health care service by the Health of Nations Outcome Scale (HoNOS), a 5-point Likert scale.[23,24] Trained nurses conducted the Positive and Negative Symptom Scale for Remission (PANSS-R) interview to assess whether the patients' psychotic symptoms were in remission, which is rated on the same 7-point Likert scale as the full version of the PANSS.[25] Medication use over the past year was retrieved from medical records and confirmed with the patient.

We included patients with schizophrenia or a related psychotic disorder (DSM-IV codes 295.4 - 295.9, 297.1, 298.8 and 298.9), who completed the SRA and used one of the following antipsychotics for at least one month prior to the interview: haloperidol, risperidone, olanzapine, clozapine, quetiapine or aripiprazole.

RATING OF EMOTIONAL EXPERIENCES The SRA has 74 items and showed a good test-retest reliability and validity in patients with schizophrenia.[21] The SRA was rated on a three-point scale (no / yes, mild / yes, severe). Factor analysis of the SRA has demonstrated that emotional experiences in response to antipsychotic medication can be separated into the dimensions flattened affect and depressive symptoms (Lako et al., 2012 *submitted*).[26] Flattened affect was measured by the four statements: "my emotions are dull", "my emotions are too dull", "I am less emotional" and "my thoughts are subdued"; and depressive symptoms by "I feel down" and "I feel more depressed"

attributed to antipsychotics. We evaluated the concurrent validity of the sum scores on flattened affect and depressive symptoms with two observational measures. We therefore calculated the correlation between flattened affect score on the SRA with the score on observed "blunted affect" (N1) by the PANSS-R; and the correlation between the depressive symptom score on the SRA with the outcome on the HoNOS depression-item. For further analyses, we used dichotomized scores: flattened affect was considered present when a patient responded all four statements about flattened affect with "yes" to a mild or severe degree; depressive symptoms were present when a patient responded both items for depression with "yes" to a mild or severe degree.

ANTIPSYCHOTIC D_2 RECEPTOR AFFINITY AND OCCUPANCY Patients using antipsychotic mono-therapy were grouped according to four levels of affinity [K_i] for the dopamine D_2 receptor of their antipsychotic: high for haloperidol and risperidone (K_i<1nM), medium for olanzapine (1<K_i<10nM), weak for clozapine and quetiapine (K_i>10nM).[16,27] The fourth category consisted of aripiprazole, which has a high but partial affinity for the D_2 receptor (K_i<1nM), because of both agonistic and antagonistic effects at the D_2 receptor.[28]

The level of D_2 receptor occupancy of each individual subject was estimated by applying dose-occupancy equivalents to the daily dose as described by Lako (2012).[29] The doses of antipsychotic depot preparations were first converted into oral daily dose values.[30] The relationship between occupancy and the log odds of emotional experiences was not linear. Therefore the continuous variable was categorized into three levels of occupancy, each containing 33% of the cases. The daily dose of patients was additionally expressed as the defined daily dose (DDD) according to the WHO,[31] by dividing the prescribed daily dose (PDD) by the DDD (PDD/DDD).

For patients using two or more antipsychotics, the level of D_2 receptor occupancy was estimated for each antipsychotic, by applying the dose-occupancy equivalents as described above.[29] The level of occupancy for bromperidol, fluphenazine, flupenthixol, pimozide and zuclopenthixol was estimated by applying dose-occupancy equivalent for haloperidol (the daily dose of zuclopenthixol was first divided by five).[30] Occupancy could not be estimated for patients using chlorprothixene, penfluridol, perphenazine, pipamperone or sertindole. For each patient, we selected the highest level of occupancy, in order to compare mean levels of occupancy between antipsychotic

combination therapy and monotherapy. The cumulative daily dose was expressed as the sum of the (PDD/DDD) ratio for each combination of antipsychotics.[31]

STATISTICS Categorical variables were tested using a chi-square test. Continuous variables were not normally distributed and were therefore assessed by the non-parametric Mann-Whitney U test. Correlations were calculated using Spearmans' correlations. The association of altered emotional experiences with the level of antipsychotic D_2 receptor affinity and the estimated level of dopamine D_2 receptor occupancy was quantified using logistic regression analysis. Dependent variables were "flattened affect" and "depressive symptoms". The levels of affinity, occupancy as well as the individual six antipsychotics were entered as categorical variables. These measures of dopamine involvement were first entered separately in two models for patients on antipsychotic monotherapy. Next, we built a regression model with both affinity and occupancy entered simultaneously to study their independent associations with altered emotional experiences, i.e. adjusted for each other. Further, we studied a potential interaction effect between affinity and occupancy by adding their product term as an independent variable to the final model. The effects of individual antipsychotics were compared by entering the six antipsychotics as categorical independent variable with haloperidol as reference category in an additional model. In a separate analysis we compared the effect of antipsychotic monotherapy with combination therapy on both altered emotional experiences. The goodness of fit of each model was evaluated using the Hosmer-Lemeshow test. Statistical analyses were performed using Statistical Package for Social Sciences (PASW-18). A two-tailed p-value of $p<0.05$ was accepted as statistically significant.

SUBJECTS Out of n=2241 patients with psychotic disorders, n=142 (6%) patients were antipsychotic free, n=200 (9%) did not use one of the selected antipsychotics, n=36 (2%) had incomplete information on antipsychotic dose and n=565 (25%) of the patients did not complete (the selected items of) the SRA questionnaire. In total, n=1298 patients were included in the study (Table 1), of whom=302 (23%) perceived flattened affect and n=212 (16%) depressive symptoms in response to antipsychotic treatment. Of note, n=103 (8%) of all included patients reported both experiences in response to antipsychotics. Male patients perceived flattened affect, but not depressive symptomatology, more frequently in response to antipsychotics than female patients ($x^2(1) = 4.80$, $p<0.05$). Patients who received antidepressants had a higher probability of attributing depressive symptoms ($x^2(1) = 6.60$, $p<0.01$), but not flattened affect to antipsychotics. Perceived flattened affect and depressive symptoms in response to antipsychotic treatment correlated weakly with observational measures of respectively flattened affect (PANSS-N1; $r = 0.11$, $p<0.01$) and depressive symptoms (HoNOS; $r = 0.22$, $p<0.01$), as rated for respectively n=1260 (97%) and n=1072 (83%) of the patients.

ANTIPSYCHOTIC MONOTHERAPY Antipsychotic monotherapy was used by n=1010 (78%) patients (Table 2). Depot formulations were used by (n=34; 40%) of the haloperidol users and (n=92; 31%) of the risperidone users. The level of D_2 receptor occupancy among patients with antipsychotic mono-therapy was distributed over the following three intervals: [0.1 - 48.3%]; [48.3 – 71.1%]; [71.1 – 89.0%]. Logistic regression showed no relationship between antipsychotic D_2 receptor affinity and altered emotional experiences in patients using antipsychotic mono-therapy. There was neither a relationship when corrected for binding affinity, nor an interaction effect between binding affinity and D_2 receptor occupancy and altered emotional experiences. In a comparison of all six individual antipsychotics, patients treated with quetiapine appeared to be less likely to report depressive symptoms compared to haloperidol, but this difference was not significant ($x^2(5) = 8.45$, OR [95%CI] = 0.392 [0.145 – 1.057]). None of the Hosmer-Lemeshow tests were statistically significant indicating no major deviations in the subgroups of the logistic models.

ANTIPSYCHOTIC COMBINATION THERAPY Antipsychotic combination therapy was prescribed for n=288 (22%) of the patients, of which n=20 patients used a

combination of three antipsychotics. Most frequently prescribed were combinations with clozapine (n=42; 49%) or depot preparations (n=67; 23%). The maximal level of estimated D_2 receptor occupancy was determined for n=275 (95%) of the patients using combination therapy. The remainder used medication for which no dose-occupancy equivalents were available. The mean D_2 receptor occupancy for patients on combinations (74%; SD11.5) was higher than for patients on mono-therapy (58.0%; SD19.8; $p<0.001$), see Table 2. In addition, patients using combination therapy had higher mean PDD/DDD ratios than patients using antipsychotic monotherapy ($p<0.001$). Patients using antipsychotic combination therapy were more likely to attribute depressive symptoms to their antipsychotic medication ($x^2(1) = 4.47$, OR [95%CI] = 1.443 [1.033 – 2.015]), but not flattened affect. This effect remained significant when adjusted for gender and antidepressant use ($x^2(3) = 10.98$, OR [95%CI] = 1.420 [1.015 – 1.986]).

We investigated the relationship between altered emotional experiences and antipsychotic D_2 receptor affinity and occupancy in a large sample of patients with psychotic disorders. The antipsychotics that were used in the sample represented a wide range of D_2 receptor affinities, including quetiapine, clozapine and aripiprazole. The main finding was that patients using antipsychotics with weak affinity for the D_2 receptor were as likely to attribute altered emotional experiences to their antipsychotics as patients using antipsychotics with higher D_2 receptor affinities. Although a trend of a reduced risk to induce depressive symptoms was observed for quetiapine compared to haloperidol, potential differences between antipsychotic monotherapy treatments in altered emotional experiences may be marginal in clinical practice. Previous associations between antipsychotics and altered emotional experiences have predominantly been demonstrated in patients receiving relatively high doses of antipsychotics with high affinity for the D_2 receptor and high corresponding levels of occupancy,[9,12,32] but not in patients using the average dosages of these antipsychotics.[14] In our sample, patients using antipsychotics with high affinity for the D_2 receptor received recommended doses of about 4 mg haloperidol or risperidone, corresponding with intermediate levels of estimated D_2 receptor occupancy (below 90%).[33,34] Possible ceiling effects were therefore difficult to detect in patients using antipsychotics with high affinity. Perhaps current prescription behavior of antipsychotics with high D_2 receptor affinity has been adjusted to the side effect profile.

The increased likelihood of patients using antipsychotic combination therapy attributing depressive symptoms to antipsychotics compared to patients using monotherapy suggested involvement of D_2 receptor occupancy. The cumulative daily dose of most patients using antipsychotic combination therapy was high and exceeded, in line with previous studies,[35,36] a rate of 1.5 times the Defined Daily Dose of the WHO.[31] Consequently their estimated level of D_2 receptor occupancy was high (>90%), which may support a relationship between high levels of D_2 receptor occupancy and altered emotional experiences.[11-14] A detailed investigation of D_2 receptor occupancy as effect moderator in the relationship with these altered emotional experiences was however difficult in patients using antipsychotic combination therapy, because the combinations were diverse and their interactions may have distinct effects on receptor occupancy. The current results demand more study of the risks and benefits of combination therapy.

An alternative theory proposes that the affinity of second generation antipsychotics for the serotonin 5-HT_{2A} receptor reduces altered emotional responses by having antidepressant effects.[37-39,40] First generation antipsychotics lacking affinity for this receptor would be more likely to have depressogenic effects.[41] Others suggest that the serotonergic modulation of the dopamine system cannot compensate for the dopamine receptor blockade by second generation antipsychotics.[18] The serotonin hypothesis is under debate, since recent studies failed to detect a differential effect between antipsychotics in the treatment of depressive symptomatology.[42-44] Likewise, our study neither found differences between users of first and second generation antipsychotics on emotional experiences. Thus potential antidepressant effects may not be dependent on serotonin transmission alone.[45]

Altered emotional experiences in response to antipsychotics were investigated from the patient's perspective. The agreement with observational measures of emotional experiences was low, which may underline the differences between self-report and interview assessment.[38,46] Self-report may be preferred for the rating of emotional experiences, since some parts of the patients' affective state are difficult to measure by observational ratings and the patients' attribution of treatment effects has found to be predictive for satisfaction and adherence to their treatment.[47,48] A potential limitation of our study was that we estimated D_2 receptor based on dose equivalents, instead of *in vivo* patients occupancy measures of the patients. A simulation study that incorporates the inter-individual variability in occupancy values for a given dose,[29] could evaluate whether our distribution of antipsychotic doses was sufficient to detect clinically relevant effects.

To conclude, our study showed that a considerable number of patients with schizophrenia attributed altered emotional experiences to their antipsychotic medication. We could not confirm an association between these experiences and the level of D_2 receptor affinity or occupancy in patients with antipsychotic monotherapy, possibly because the dosing strategies were adequate. The increased likelihood of patients using antipsychotic combination therapy attributing depressive symptoms to their antipsychotics, however, suggested a dose-relationship with D_2 receptor occupancy. We would recommend being cautious with prescribing combination therapy to avoid depressive symptoms in response to antipsychotics.

TABLE 1. Patient characteristics (N=1298).

	N or mean	% or SD
Gender, male	901	69%
Years of age (mean;SD)	40.0	11.0
Years of illness (mean; SD)	13.4	9.9
Treatment Status		
Outpatients	791	62%
Inpatients (acute & chronic)	245	19%
Sheltered Housing Facilities	251	20%
Diagnosis		
Schizophrenia diagnosis	919	70%
Schizoaffective disorder	155	12%
Other psychotic disorder	224	7%
Psychotic symptoms (PANSS-R)		
Positive (mean; SD)	2.3	1.1
Negative (mean; SD)	2.1	1.0
Antipsychotic medication		
Monotherapy	1010	78%
Combination therapy	288	22%
Co-medication (number; SD)	2.0	2.2
Antidepressants	348	27%
Benzodiazepines	303	23%
Anticholinergics	168	13%
Moodstabilizers	71	6%
Sleep medication	134	10%

TABLE 2. Antipsychotic treatment was categorized into four levels of D_2 receptor affinity or combination therapy (N=1298). The number of patients attributing flattened affect or depressive symptoms to antipsychotics was given for each treatment group. PDD/DDD = mean prescribed daily dose divided by defined daily dose; D_2R Occ. = mean estimated level of D_2 receptor occupancy; for patients using antipsychotic combination therapy only the mean maximal level of each combination was displayed as indicated by an asterisk (*); Antidepr. = antidepressant use; D_2R Affinity = D_2 receptor affinity class.

Antipsychotic (N)	Dose, mg [mean;SD]	PDD/DDD [mean]	D_2R Occ. [mean %]	Antidepr. [N,%]	Flattened [N,%]	Depressive [N;%]	D_2R Affinity (N)	Flattened [N,%]	Depressive [N;%]
Haloperidol (57)	4.07 (±4.24)	0.9	74%	15 (26%)	16 (28%)	10 (18%)	High (355)	87 (25%)	54 (15%)
Risperidone (298)	3.69 (±3.72)	0.8	66%	58 (19%)	71 (24%)	44 (15%)			
Olanzapine (276)	13.7 (±7.3)	1.4	61%	77 (28%)	55 (20%)	43 (16%)	Medium (276)	55 (20%)	43(16%)
Clozapine (197)	317 (±163)	1.1	42%	60 (30%)	45 (23%)	38 (19%)	Weak (301)	66 (22%)	46 (15%)
Quetiapine (104)	486 (±315)	1.2	26%	34 (33%)	21 (20%)	8 (8%)			
Aripiprazole (78)	16.8 (±7.0)	1.1	85%	15 (19%)	17 (22%)	10 (13%)	Partial (78)	17 (22%)	10 (13%)
Mean monotherapy (1010)		1.1	58%	259 (26%)	225 (22%)	153 (15%)			
Combination therapy (288)		~2.3	74%*	89 (31%)	77 (27%)	59 (21%)			

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9

General discussion

SUMMARY BACKGROUND OF THE THESIS

Patients with schizophrenia have a high burden of disease. Many of them suffer from co-morbid depressive symptoms, which may further increase the burden of disease. Depressive symptoms in these patients might particularly lead to functional limitations in the real world. Thus depression is an important treatment target for disability reduction. The overlap between depressive symptoms and other psychotic symptoms complicates their recognition in clinical practice. Misclassification leads to under- or over-recognition of depressive symptoms in this population. Correct identification of depressive symptoms is important in disease management of these patients. Depression rating scales help the clinician to recognize depressive symptoms in practice. Many (self-report) depression instruments are available to measure depressive symptoms, but there is no overview of the reliability and validity of these depression instruments in patients with schizophrenia. Depressive symptoms can be a side effect of antipsychotic medication, but it is currently unclear whether depressive symptoms in response to antipsychotics represent a separate symptom dimension from other (affective) side effects. Furthermore, there is a lack of dose-occupancy equivalents describing antipsychotics with weak affinity for the D_2 receptor. Finally, the relation between depressive symptoms and antipsychotic D_2 receptor affinity and occupancy needs additional investigation for a wide range of antipsychotics, including antipsychotics with weak affinity for the D_2 receptor. More understanding of (secondary) depressive symptoms aids the clinician in finding an optimal treatment strategy for depressive symptoms.

This thesis investigated the recognition of depressive symptoms in patients with schizophrenia by:

- Describing the course of depressive symptoms in relation to the prescription patterns of antidepressants. Comparing the psychometric properties of depression instruments that can be used for the monitoring of depressive symptoms in clinical practice of patients with schizophrenia. Exploring the validity of self-report instruments that can be used for the monitoring of depressive symptoms of patients with schizophrenia.
- Investigating the involvement of antipsychotic D_2 receptor affinity and occupancy in depressive symptoms attributed to antipsychotics. This involved the validation of a method to measure depressive symptoms in response to antipsychotics and the development of dose equivalents to estimate the level of dopamine D_2 receptor occupancy for a given antipsychotic dose.

COURSE OF DEPRESSIVE SYMPTOMS OVER TIME

In order to gain insight into the course of depressive symptoms in relation to antidepressants, we followed patients with schizophrenia over two years as described in Chapter 2. Our study showed that depressive symptoms are highly prevalent and persistent in patients with schizophrenia. Patients with more severe psychopathology had an increased risk to develop depressive symptoms.

Two out of five patients used antidepressants. This prescription of antidepressants is high, and in line with other European studies.[1-3] We further demonstrated that the majority of patients continued the use of antidepressants once prescribed, even if no depressive symptoms were observed. Their indication of antidepressants could have been prophylaxis,[4,5] negative symptoms or anxiety or it may indicate overprescribing. A previous survey among clinicians suggested that antidepressants are not always prescribed according to the treatment guidelines,[6] hence overprescription may occur in the treatment of patients with sub-syndromal depressive symptoms.[7] As a limitation of the depression rating scale used in our study, we were unable to analyze a relationship with the severity of depressive symptoms.

Of the patients having depressive symptoms at baseline, the majority kept having depressive symptoms despite continuing antidepressant therapy. Moreover, we identified the use of co-medication as a predictor for patients to keep having depressive symptoms, instead of remitting from depressive symptoms. Although this observational study could not evaluate the effectiveness of antidepressants in patients with schizophrenia, we know from two recent systematic literature reviews that the effectiveness of antidepressants is unclear in this population.[8,9] We therefore recommend close monitoring of the treatment of patients with schizophrenia and depressive symptoms, particularly in those patients using co-medication.

RECOGNITION OF DEPRESSIVE SYMPTOMS IN SCHIZOPHRENIA

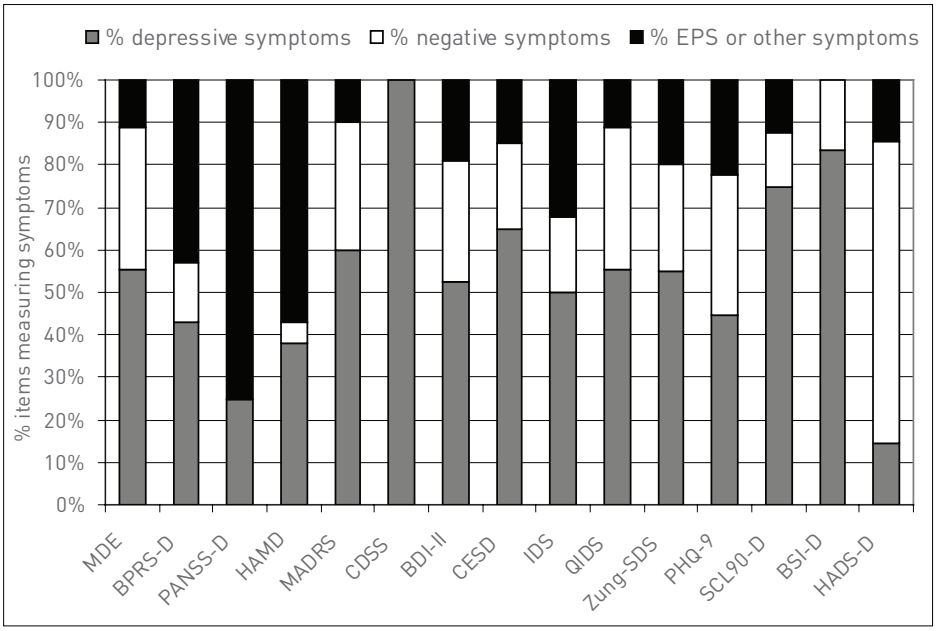
OVERVIEW OF DEPRESSION INSTRUMENTS The review in Chapter 3 aimed to guide the clinician in choosing a suitable instrument for the measurement of depressive symptoms in patients with schizophrenia. Based on systematic literature review, we compared psychometric properties of six popular depression instruments

with tested validity in patients with schizophrenia. The Calgary Depression Scale for Schizophrenia (CDSS) is the only depression instrument specifically developed for use in populations with schizophrenia. Three other instruments included for evaluation were primarily developed for use in depressed populations and another two were depression subscales of psychotic symptom rating scales. We demonstrated that the CDSS interview outperformed other depression scales on discriminative validity for the negative symptom dimension and other aspects of reliability and validity in patients with schizophrenia. The other depression instruments were more likely to misdiagnose negative symptoms as depressive symptoms than the CDSS. This was illustrated by analysis of the content of the depression instruments. All depression scales, except for the CDSS, contained one or more items tapping into negative symptoms of schizophrenia (Figure 1).

Another outcome of the study was the gap in literature regarding validated self-report depression instruments in this population. No self-report depression instrument was especially designed for use in patients with schizophrenia. The only self-report instrument that was tested on a full set of psychometric properties was the Beck Depression Inventory (BDI), but its predictive validity to detect cases of depression was poor in patients with schizophrenia. We aimed to find a valid self-reported depression instrument as an alternative for the BDI in patients with schizophrenia based on available literature. Previous studies describing psychometric properties of the Quick Inventory for Depressive Symptoms (QIDS-SR_{16})[10] and the Center for Epidemiologic Studies-Depression (CES-D)[11] in patients with schizophrenia were limited, but promising.[12-14] Evaluation of the composition of these instruments demonstrated that especially for the CES-D a minimal number of items tap into negative symptoms, compared to other self-report depression instruments (Figure 1). The concurrent validity of the $QIDS_{SR16}$ and the CES-D self-report scales was compared with the CDSS as the golden standard depression rating scale for patients with schizophrenia in Chapters 4 & 5.

The percentage of items covering the core depressive symptoms was compared with the percentage of items potentially overlapping with negative symptoms, EPS or other psychotic symptoms. This figure is an extended version of Table 2 in Chapter 3, including depression instruments that were excluded from analysis because a lack of tested psychometric properties in patients with schizophrenia.

FIGURE 1. The item composition of depression instruments.



Abbreviations: EPS = Extrapyramidal Symptoms; DSM-IV – Diagnostic and Statistical Manual of Mental Disorder – 4th Edition; MDE = DSM-IV criteria for Major Depressive Episode

Multidimensional psychotic symptom scales (observer rated): BPRS = Brief Psychiatric Rating Scale – Depression subscale; PANSS = Positive And Negative Syndrome Scale – Depression subscale

Observer-rated depression scales: HAMD = Hamilton rating scale for Depression; MADRS = Montgomery Asberg Depression Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia

Self-rating depression scales: BDI-II = Beck Depression Inventory-II; CESD = Center of Epidemiologic Studies – Depression; Zung-SDS = Zung Self-rating Depression Scale; IDS = Inventory for Depressive Symptoms; QIDS = Quick Inventory for Depressive Symptoms; PHQ-9 = Patient Health Questionnaire- 9

Multidimensional self-rating scales: SCL90-D = Symptom Checklist-90 – Depression subscale; BSI-D = Brief Symptom Inventory – Depression subscale; HADS-D = Hospital Anxiety and Depression Scale – Depression subscale

SELF-REPORT MEASURES OF DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA The results described in Chapter 4 suggest that not all depression instruments are suitable for use in patients with schizophrenia. Although the QIDS-SR_{16} well discriminated depressive symptoms from negative symptoms and

extrapyramidal symptoms (r=<0.30), the QIDS-SR_{16} agreed only moderately with the CDSS as golden standard depression rating scale (r=0.44) in a large sample of patients with schizophrenia or related psychotic disorders. This moderate correlation suggests differences with the CDSS.

The scores on the QIDS-SR_{16} dimensions measuring the physical symptoms of depression were relatively high and discordant with the CDSS in this population. This was in most cases driven by the items 'excessive sleep' and 'increased appetite', which may reflect side effects of antipsychotics,[15,16] and hence not necessarily be related to the 'physical' symptoms of depression.[17] Post hoc analysis confirmed that those patients using antipsychotics with high antagonistic affinity for the histamine receptor (olanzapine or clozapine) were more likely to report increased appetite and excessive sleep than patients using other antipsychotics. It can be argued that antipsychotic side effects confounded changes in sleep and appetite as measured by the QIDS-SR_{16} in the current sample. In contrast, the CDSS measures 'early awakening' and 'morning depression' as a proxy for the physical symptoms of depression, in a way less sensitive to confounding by antipsychotic side effects. Thus, not only the measurement of extrapyramidal side effects, but also sedative effects from antipsychotics should be avoided in the assessment of depressive symptoms in patients with schizophrenia. Another symptom that is well covered by CDSS and the CES-D, but not the QIDS-SR_{16} is hopelessness. Patients with schizophrenia may be prone to psychological depressive symptoms like hopelessness and self-depreciation, possibly related to demoralization in response to the severe mental illness.[18] In conclusion, we would not recommend to measure depressive symptoms by the QIDS-SR_{16} in patients with schizophrenia or psychotic disorders.

Chapter 5 showed that the CES-D is a promising self-report for the monitoring of depressive symptoms in patients with psychotic disorders. In contrast to the QIDS-SR_{16}, the CES-D agreed well with the gold standard rating scale (CDSS) for depressive symptoms in this population (r=0.70). This is a remarkable result, since the CES-D is designed to measure mainly the sub-syndromal symptoms of depression. The CES-D does not cover one of the more severe DSM-IV criteria for depression, suicidal ideation. Furthermore, the CES-D measures some symptoms that are not specific for depression, but for a general feeling of distress such as 'I felt lonely' and 'I talked less than usual'. Hence CES-D scores may be sensitive to changes in other pathological co-morbidities, in this case psychosis. We therefore recommended an additional clinical

interview as follow-up assessment for patients with high scores indicative for depression.

The good internal consistency of the CES-D in patients with psychotic disorders suggests that the patients are able to rate their depressive symptoms in a reliable way.[19] We noticed that the patients experienced minimal effort to complete the CES-D questionnaire. Instead, previous studies reported that at least 10% of patients with schizophrenia had difficulties to complete the BDI questionnaire.[20,21] The answer categories of the BDI consist of four statements, which differ for each question, thus all these statements need to be read separately. Patients may find it easier to complete a uniform Likert scale with a visual degree of severity like the CES-D, especially those patients with concentration problems associated with schizophrenia.[21] The current results suggest that the CES-D is a feasible self-report instrument for the measurement of depressive symptoms in patients with schizophrenia. As a limitation of this study, we were not able to determine the discriminative validity of the CES-D to distinguish depressive symptoms from negative symptoms or extrapyramidal symptoms. Future research will be needed to address this issue.

One of the lessons we learned, is that there is a lot of variation in the reliability and validity of depression instruments in patients with schizophrenia. In view of the upcoming DSM-V, monitoring the severity of symptom dimensions over time may become more important than predicting dichotomous outcomes. This thesis therefore focused on instruments to monitor (sub-syndromal) depressive symptoms and not on diagnostic classifications predictive for a major depressive episode. Still, we feel obliged to address some inconsistencies in the prevalence rates of depressive symptoms reported in the previous Chapters. According to the CDSS, 10-17% of the patients were potential cases of depression in our samples (Table 1). This was in sharp contrast to the prevalence rates based on clinician ratings (Chapter 2) and self-report by the QIDS-SR_{16} and CES-D (Chapter 4 and 5), of which the percentage of patients with depressive symptoms indicative for mild to severe depression varied from 38 to 52%. The clinician ratings used in Chapter 2 were no validated measures of depressive symptoms in this population. The instructions for these ratings did not help the clinician to adequately distinguish depressive symptoms from the negative symptoms in this population, which may have resulted in an overestimation of depressive symptoms in the clinical practice described in Chapter 2. Since we expect that the in-depth CDSS interview provides more precise information than the clinician ratings and self-report measures, the actual prevalence of (mild) depression is most

likely between 10 and 17% in the populations with psychotic disorders studied in this thesis.

An explanation for the inflated prevalence rate of depression by self-report may be that subjects tend to agree with statements as presented (acpuiescence bias). Or subjects may have a preference to fill out either the left or the right answer categories in a way that symptoms can become over-reported.[22] The CES-D is, however, designed to avoid this bias, since positive and negative statements are mixed throughout the questionnaire. Another explanation could be the choice of the cut-off scores of the self-report scales. The cut-off scores indicative for depression as proposed by investigators of the QIDS-SR_{16}[11] and the CES-D[23] were meant for use in depressed populations. Yet, the predictive validity of these cut-off scores to detect cases of (mild) depression has not been tested in separate populations with psychotic disorders. Perhaps these cut-off scores are too sensitive to detect cases of depression and identify too much false-positive cases of depression in patients with psychotic disorders. Since depression diagnoses were not systematically recorded in both studies, we were not able to determine a cut-off score of the QIDS-SR_{16} with an optimal sensitivity and specificity to detect cases of depression in this population. Future research may be needed to find a more optimal cut-off score for the CES-D, to optimize the predictive validity and interpretation of the CES-D in this population. The results of the study on the QIDS-SR_{16} do, however, not advocate future application of the QIDS-SR_{16} in research or clinical practice of patients with schizophrenia.

TABLE 1. The prevalence of (mild) depression in Chapter 4 and 5.

Depression instrument	Cut-off score	Sample	Prevalence
Clinician rating	≥ 2 out of 3	ROM (2006), Chapter 2	43%
CDSS (observer rated)	≥ 5 out of 27	GROUP (2011), Chapter 4	17%
QIDS-SR (self-report)	≥ 6 out of 27	GROUP (2011), Chapter 4	52%
CDSS (observer rated)	≥ 5 out of 27	PHAMOUS (2011), Chapter 5	10%
CES-D (self-report)	≥ 15 out of 60	PHAMOUS (2011), Chapter 5	38%

CONCEPTUAL ISSUES OF DEPRESSION IN PATIENTS WITH SCHIZOPHRENIA The concept of depressive symptoms in schizophrenia differs from a major depressive episode in a depressed population or the general population. We demonstrated that

due to overlap with other psychotic symptoms and side effects from antipsychotics, only five of the nine DSM-IV criteria for depression are –partially– useful to detect depressive symptoms in patients with schizophrenia. Consequently, the item composition of a depression instrument especially designed to measure depressive symptoms in patients with schizophrenia should differ from instruments designed for depressed populations, as illustrated by (Figure 1). Another complicating factor in the recognition of depressive symptoms is that the general concept of depression continues to be under debate for consecutive DSM editions (http://www.dsm5.org). For example, the content of the HAM-D reflects that early criteria for depression focused more on physical and less common symptoms such as diurnal variation, which are currently considered less relevant.[24] Although concepts and views have changed, the CDSS covers these depressive symptoms in an acceptable way. The CDSS well avoids the measurement of negative symptoms and the effects of antipsychotics on extrapyramidal symptoms, sleep, and appetite may not meaningfully affect the interpretation of the outcome of the CDSS (see above). A possible limitation may be that guilt is over-represented by two items, since the item about worthlessness already covers this dimension. In absence of a depression instrument especially developed for patients with schizophrenia, the CES-D is a feasible instrument to monitor depressive symptoms. Future research is needed to evaluate a more optimal cut-off score in patients with schizophrenia. Ideally a new self-report scale may need to be developed to assess depressive symptoms in this population.

SUGGESTIONS FOR A NEW SELF-REPORT DEPRESSION INSTRUMENT The symptom dimensions that should be covered by a self-report depression instrument, especially designed for use in a population with psychotic disorders, are discussed here. In our opinion such a self-report depression instrument should address the following symptoms: 1) depressed mood or feeling sad, 2) hopelessness, 3) suicidal ideation 4) worthlessness but not guilt. Since the patient may have difficulties to disentangle delusional feelings of guilt from ruminating over minor past failures as part of depression, it was felt to be inappropriate to measure guilt by self-rating. Changes in 5) sleep and 6) appetite can be included, as long as they measure a decrease in these activities (early wakening), to avoid ambiguous responses due to antipsychotic side effects. Reverse changes in these physical symptoms (increased sleep and appetite) are characteristic of "atypical" depression and common in 40% of the depressed population.[17] Other symptoms characteristic of atypical depression

may serve as a better proxy for depression in patients with schizophrenia, such as interpersonal rejection sensitivity, mood reactivity (i.e., mood brightens in response to actual or potential positive events) or diurnal variation (morning depression). If needed, the instrument can be expanded with symptoms commonly associated with depression, including cognitive symptoms (e.g. pessimism about the future or feelings of loneliness) and psychological symptoms (e.g. crying spells or an exaggerated sense of frustration about minor matters). Examples of statements that tap into these symptoms can be found in the CDSS, CES-D, Symptom Checklist-90 depression subscale (SCL-90-D) and Zung Self-rating Depression Scale (Zung-SDS).[25,26] Finally, symptoms reflecting DSM-IV criteria for depression that overlap with negative symptoms or side effects from antipsychotics should be avoided in the measurement of depressive symptoms in patients with schizophrenia, i.e. anhedonia, fatigue, indecisiveness/lack of concentration, psychomotor agitation/retardation and increased sleep, appetite and weight.

DEPRESSIVE SYMPTOMS ATTRIBUTED TO ANTIPSYCHOTICS

SUBJECTS' RESPONSE TO ANTIPSYCHOTICS-34 The main outcome of the study in Chapter 6 is that we developed the SRA-34 as quick tool to measure depressive symptoms, amongst other experiences, in response to antipsychotics. The SRA-34 addresses a wide range of both desired and undesired effects that patients may experience in response to their antipsychotics. Although we wished to reduce the number of items of the SRA-74 as much as possible, the clinical reality of heterogeneous side effects did not allow us to further reduce the SRA-34 while maintaining a meaningful set of antipsychotic effects. The added value of the SRA 34 to existing instruments lies in the measurement of important social and mental experiences,[27] besides the physical adverse effects of antipsychotics.[28,29] Our observation that most patients appeared rather satisfied about their medication, despite the numerous side effects, underlined the clinical importance of measuring both desired and undesired effects. A secondary advantage of asking the patient about the desired effects is that it recalls them to the benefits of taking medication, which may indirectly improve the patients' adherence with their antipsychotic medication.[30] Investigating antipsychotic effects from the patient's perspective by means of the SRA-34 may help the clinician to understand the patients' satisfaction and reasons for compliance with their medication.[31] We would advocate monitoring of the patients experience with antipsychotics using the

SRA-34 in daily practice as well as clinical trials.

Our factor analysis of the Subjects' Response to Antipsychotics (SRA-74) demonstrated that patients with schizophrenia frequently attributed depressive symptoms to their antipsychotics, independent of other drug-induced emotional experiences or EPS. The identification of the depressive dimension in response to antipsychotics was novel, while most other symptom dimensions identified by factor analysis were in line with the original subscale structure of the SRA-74.[32] Our large sample enabled us to detect the coherence between two depression items, which were previously categorized as miscellaneous effects (i.e. Because of the antipsychotic medication I feel "more depressed" / "down"). These two depression items can be used to study the relation of depressive symptoms and antipsychotics with more detail than previous studies. Previous studies investigated the relation between depressive symptoms and antipsychotic D_2 receptor blockade by a mix of emotional experiences,[33] or clinician ratings of depressive symptoms.[34,35]

METHODOLOGICAL CHALLENGES IN THE DEVELOPMENT OF QUESTIONNAIRES

In the development of the SRA-34 questionnaire to assess experiences in response to antipsychotics, we choose to perform exploratory factor analysis (EFA) on the SRA-74 (Chapter 6). The reasoning behind EFA was that we had no *a priori* assumptions about the latent structure of the questionnaire. Most other dimensional scaling techniques are based on *a priori* assumptions, such as structural equation modeling,[36] and inter-item correlations.[32] Based on the latent structure of the SWN for well-being,[36,37] we expected the single subscale for desired effects of the SRA-74 to be multi-dimensional,[32] yet the number or content of these dimensions was to be defined. We also expected additional clustering within the subscale for miscellaneous effects, for example between anticholinergic side effects such as constipation and dry mouth.[29] Our EFA confirmed our hypothesis about the multidimensionality of the desired effects. Furthermore, two of the initial 'miscellaneous' depressive symptoms were identified as a new symptom dimension and the 'miscellaneous' problems with concentration and memory loaded on the factor for 'slowed down' behavior. As a limitation of conducting EFA on a three point scale, some other miscellaneous effects clustered into an artificial factor without a common content. Similarity analysis, based on the level of mutual information shared between variables, enabled us to visualize these shortcomings of factor analysis. Similarity analysis demonstrated that these miscellaneous effects were mutually independent. Hence, we found no latent factor

for the anticholinergic effects; perhaps these effects are not mediated by one common mechanism in patients with schizophrenia. Likewise, similarity analysis confirmed that inability to sit still (akathisia) was not associated with other extrapyramidal side effects. We would therefore recommend supporting exploratory factor analysis of a multidimensional questionnaire by visualization of the latent structure, using similarity analysis based on mutual information.

DOPAMINE INVOLVEMENT IN DEPRESSIVE SYMPTOMS ATTRIBUTED TO ANTIPSYCHOTICS

ANTIPSYCHOTIC DOSE AND DOPAMINE D_2 RECEPTOR OCCUPANCY In order to investigate the involvement of dopamine in drug-induced depressive symptoms, Chapter 7 describes a series of new dose equivalents to estimate the level of dopamine D_2 receptor occupancy based on antipsychotic dose, in absence of *in vivo* occupancy measures. Based on published imaging data, we modeled the relationship between antipsychotic dose and D_2 receptor occupancy for different doses of eight frequently prescribed antipsychotics. Of these antipsychotics, the weak dopamine antagonist quetiapine, as well as the partial agonist aripiprazole have not been modeled before. The resultant dose-occupancy functions reflect the pharmacodynamic properties of the antipsychotics,[38] since the strong dopamine antagonists (E_{max} › 90%; haloperidol and risperidone with high maximal D_2 receptor occupancy of) are easily distinguishable from the weak dopamine antagonists like clozapine and quetiapine with low maximal occupancy (E_{max} ‹ 65%).

Our meta-analysis improved the knowledge on the variability in occupancy values. We were the first to separate inter-individual variability from inter-study variation in D_2 receptor occupancy, using a non-linear mixed model. We observed high variability in occupancy values, especially for haloperidol and risperidone. For these strong dopamine antagonists, potential threshold occupancy values indicative of D_2 receptor mediated side effects should therefore be reported as ranges, rather than absolute values.[39] Although methodological disagreement between imaging studies explained a significant part of the variability in occupancy, most of the variability was explained by inter-individual variability. The high inter-individual variability in D_2 receptor occupancy implied that our antipsychotic dose equivalents, as well as the conventional dose equivalents like the Daily Defined Dose (DDD)[40] or Haldol equivalents,[41,42] are

imprecise when applied to individual cases. These inter-individual differences are most likely related to differences in metabolism or genetic background.[43] The high inter-individual variability further underlines the need for individual dosing strategies to avoid side effects in response to excessive D_2 receptor occupancy. Our dose-occupancy equivalents are optimal to study D_2 receptor mediated antipsychotic effects in a population, in case *in vivo* occupancy measures of the patients are not available. The advantage of our dose-occupancy equivalents over the conventional dose equivalents when studying D_2 receptor mediated antipsychotic (side) effects, is that dose-occupancy equivalents are based on one of the underlying mechanisms, instead of therapeutic effect.

METHODOLOGICAL CHALLENGES IN META-ANALYSIS OF PUBLISHED OCCUPANCY DATA Our review of D_2 receptor occupancy improved the modeling technique of predicting D_2 receptor occupancy based on meta-analysis of published imaging data. The relation between antipsychotic dose or plasma and D_2 receptor occupancy can be described by an asymptotic Michaelis-Menten function (Figure 2).[44,45] Some authors assumed that infinite doses of antipsychotics could occupy maximal level of 100% of the dopamine D_2 receptors by fixing the horizontal asymptote to 100%,[33] although some antipsychotics may never reach 100% occupancy, even when given in high doses.[46] The plasma-level based models of Uchida demonstrated that models with an unconstrained maximum level of occupancy outperformed the predictive validity of models with a fixed horizontal asymptote for infinite antipsychotic doses.[47] We further improved those unconstrained models by assuming that also the 95% confidence interval around the estimated maximal level of D_2 receptor occupancy should remain below the theoretical level of 100% occupancy. By logistic transformation of the occupancy data, we avoided that our models would predict theoretically impossible occupancy values above 100%. Another benefit of logarithmic transformation of the data was that inter-study variation could be included as a random effect in the model. Our techniques can also be applied to models estimating the level of occupancy based on plasma levels instead of antipsychotic dose. Estimations based on plasma levels may be more precise than estimations based on antipsychotic dose, since plasma level varies widely between patients for each individual antipsychotic dose.[48] In case neither *in vivo* D_2 receptor occupancy levels nor plasma levels can be obtained in a population with schizophrenia, the current dose equivalents can predict their median level of D_2 receptor occupancy based on antipsychotic dose.

A possible limitation is that our dose-equivalents are designed to estimate the level of D_2 receptor occupancy in the patients using antipsychotic monotherapy. The dose-equivalents cannot reliably estimate the cumulative level of D_2 receptor occupancy in patients with schizophrenia. Given that antipsychotics may interact and antipsychotics may theoretically occupy 100% of the D_2 receptors, the effect of combining antipsychotics on D_2 receptor occupancy may not simply be additive. Alternatively, the cumulative dopaminergic load of a patient could be expressed by a risk score, analogous to the formula that describes the anticholinergic load of medications.[49] The development of measures of the dopaminergic load in patients using antipsychotic combination therapy can be useful for further investigation of a possible relation with antipsychotic-induced depressive symptoms.

DOPAMINE INVOLVEMENT IN DEPRESSIVE SYMPTOMS ATTRIBUTED TO ANTIPSYCHOTICS In contrast to previous hypotheses,[50,51] Chapter 7 suggests that antipsychotic-induced depressive symptoms are not related to antipsychotic D_2 receptor affinity or occupancy in patients using antipsychotic monotherapy. We studied altered emotional experiences in a large and naturalistic study sample of patients with schizophrenia, using antipsychotics with distinct D_2 receptor affinities. Although we observed a reduced risk of inducing depressive symptoms at trend level for quetiapine, potential differences between (types of) antipsychotics in depressive symptoms attributed to antipsychotics may not be robust in clinical practice. The strong dopamine antagonists haloperidol and risperidone were prescribed in low to intermediate doses (±4 mg), with estimated occupancy levels below the critical range of 80% occupancy.[6,52] Apparently, all prescribed antipsychotics overlapped in a level below 80% of D_2 receptor occupancy, possibly with an equal risk of emotional side effects. This lack of ceiling effects related to adequate dosing strategies of antipsychotic monotherapy may have withheld us from identifying D_2 receptor occupancy as an effect modifier/moderator in patients using antipsychotic monotherapy.

The increased likelihood of patients using antipsychotic combination therapy attributing depressive symptoms to their antipsychotics, however, suggested a relationship with excessive D_2 receptor occupancy. One out of four patients received antipsychotic combination therapy and most of them received high cumulative doses and correspondingly high estimated levels of D_2 receptor occupancy. However, we could not investigate the relationship between altered emotional experiences and

D_2 receptor occupancy for patients using antipsychotic combination therapy, since the combinations are diverse and their interactions may have distinct effects on receptor occupancy. Altogether, we would recommend being cautious with the prescription of combination therapy, especially in high doses, to avoid undesired emotional experiences in response to excessive D_2 receptor blockade.

IMPLICATIONS FOR CLINICAL PRACTICE

RECOGNITION OF DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA We would recommend the Calgary Depression Scale for Schizophrenia (CDSS) interview for the screening and monitoring of depressive symptoms in clinical practice and research (Chapter 3). The training of research nurses in the CDSS takes about half a day. Educating staff in the use of the CDSS contributes to the general knowledge of specialists in psychotic disorders about depression. In daily practice, nurses offer psychosocial interventions and education helps them to recognize which symptoms are important to recognize in an early stage of depression.[53] Also, the patient may feel better understood if a validated instrument is employed to assess their complaints.

The use of both clinician-rated and patient-reported measures in systematic routine assessment might help to gather more in-depth information on the patients' opinion and increase the patient's confidence. The involvement of patients as active partners in care is considered feasible, except in a few cases where individuals have severe cognitive dysfunction or extremely reduced insight.[54] In absence of a self-report depression instrument that is especially designed for patients with schizophrenia, we recommend the CES-D as a feasible self-report instrument to monitor the severity of sub-syndromal depressive symptoms over time. Patients with high scores on the CES-D need a follow-up diagnostic interview to identify whether depression is present. A better alternative self-report scale may need to be developed for this population. If the clinician wishes to use a multidimensional self-report instrument that includes the measurement of depressive symptoms amongst other psychopathology in patients with psychotic disorders, the SCL-90 or the BSI can be considered. The content of the depression subscales of the SCL-90 and BSI overlapped only little with other psychotic symptoms,[25,26] though additional research is needed to investigate the validity of these instruments in patients with schizophrenia.

RECOGNITION OF (EMOTIONAL) EXPERIENCES IN RESPONSE TO ANTI-PSYCHOTICS For routine monitoring of experiences in response to antipsychotics, including depressive symptoms, we advise to use SRA-34 as a quick and comprehensive screening tool. The SRA-34 is a unique instrument that addresses a wide range of desired and undesired experiences that patients may experience in response to their antipsychotics. The lay-term expression of subjective experiences based on original patient statements may appeal more to a patient than the wording based on literature and expert opinion of other instruments.[28,29] When using the SRA-34, in addition to the conventional measurement of symptom reduction by antipsychotics (PANSS or BPRS), as endpoint in clinical trials, the outcomes of the SRA-34 may need further investigation to comply with US Food and Drug Administration (FDA) Guidance for the use of patient assessments.[55]

ROUTINE OUTCOME MONITORING The recognition of depressive symptoms can be further improved by adopting depression instruments as part of annual routine monitoring (ROM). ROM may guide this diagnostic process by providing additional information about possible relapse psychosis, differential diagnoses, and multiple symptom dimensions at the same time. An example of comprehensive annual ROM is the Pharmacotherapy Monitoring and Outcome Survey (PHAMOUS), designed to monitor the mental and physical health of patients with psychotic disorders. PHAMOUS is implemented in all mental health care organizations in the North of the Netherlands and provided the data for Chapters 2, 4, 6 and 8. The rationale for this screening is that patients with schizophrenia were considered to have an increased mortality risk, possibly related to their unhealthy lifestyle[56,57] and genetic premorbidity[58] in combination with the use of antipsychotic medication.[59] Because these patients are devoid of initiative to seek help for their problems themselves, ROM may help to timely detect co-morbidities like metabolic syndrome.[60] ROM data could help the clinician to improve the patient's quality of life, e.g. by timely adjustments of (pharmaco)therapeutic interventions.[61] The longitudinal ROM data can be used for epidemiological research, as demonstrated by this thesis, to provide insight into the relation between depressive symptoms and prescription patterns of medication.

IMPROVEMENT OF TREATMENT GUIDELINES FOR DEPRESSIVE SYMPTOMS IN SCHIZOPHRENIA The NICE guideline recommends additional screening for depressive symptoms in patients with schizophrenia,[62] especially for patients in early stages. In our opinion, the guidelines should specify their advice by recommending the CDSS interview as a valid screening instrument for depressive symptoms in this population. It should be noted that further evaluation by clinical diagnostic interview is recommended for patients with high CDSS scores indicative of a diagnosis of depression. Also the effect of screening by the CDSS on outcomes in terms of relapses, hospitalizations, and suicidality may need further investigation.

There is evidence that both clinical symptom severity and risk factors independently predict the prognosis of psychopathology and identify persons at risk of a poor outcome.[63] Integrating measures of symptom severity with risk factors, such as psychopathology and co-medication (see Chapter 2) in the management of depressive symptoms, may improve individualized care.

Guidelines provide no specific recommendations for the treatment or prevention of depressive symptoms attributed to antipsychotics, besides a preference for second generation antipsychotics.[6,52,62] Since our findings suggested a relationship with depressive symptoms in patients using antipsychotic combination therapy, we would recommend being cautious with the prescription of antipsychotic combination therapy, especially in high doses. Furthermore, since we identified co-medication (benzodiazepines, antidepressants) as risk factor to have persisting depressive symptoms, we would advocate minimizing the total number of drugs in this population. More extensive research is needed to evaluate effects of lowering the number of drugs or antipsychotic doses on depressive symptoms, in order to improve the treatment guidelines for patients with schizophrenia.

BEYOND BIOLOGY A possible confounding factor in the attribution of depressive symptoms to antipsychotics we could not address in Chapter 6, was the psychological effect of using antipsychotic medication. The use of antipsychotics may involuntarily remind a patient of having a severe or disabling mental illness or intensify the stigma associated with lifelong dependence on medication, which could make patients feel incompetent and depressed.[64] This stigmatic experience has also been reported by patients using medication for chronic somatic conditions.[65] It would be interesting to

investigate whether the effect of stigma could explain part of the depressive symptoms patients attribute to their antipsychotics. In case depressive symptoms would be related to (self)stigma, the clinician may help these patients to cope with their disease by psycho-education or cognitive behavioral therapy (CBT).

A considerable number of patients with subsyndromal depressive symptoms may suffer from demoralization syndrome,[18] it may be difficult to disentangle demoralization syndrome from depression. Patients with demoralization syndrome benefit more from psychosocial approaches rather than pharmacotherapy by antidepressants. Psychosocial treatment options include cognitive behavioral therapy (CBT) to help patients to mourn their losses and cope with the disease,[66,67,68] or other forms of psychosocial treatment that help patients to address feelings of low self-esteem and hopelessness, set realistic goals, and develop skills to attain them.[69] Improving the recognition of demoralization syndrome could contribute to a better choice for effective treatment.

SOME CONCLUDING REMARKS Depressive symptoms are prevalent in patients with schizophrenia. Antidepressants are frequently prescribed and maintained in the treatment of depressive symptoms. In clinical practice, clinicians may have difficulties to adequately distinguish depressive symptoms from negative symptoms and side effects in this population. The use of validated instruments like the CDSS aids the clinician in the recognition of depressive symptoms, and may thereby prevent over-recognition or over-treatment with antidepressants.

Patients attribute depressive symptoms to their antipsychotics, independently from other altered emotional experiences. Antipsychotic combination therapy has been associated with depressive symptoms, suggesting a relationship with excessive dopaminergic blockade. A dose-response relationship with D_2 receptor occupancy could however not be confirmed in patients using antipsychotic monotherapy, probably because of cautious dosing strategies. Still, the high inter-individual differences in occupancy values for a given antipsychotic dose underline the need for individual dosing strategies. An elegant strategy to address these individual differences is shared decision making. Self-rating of experiences by short and easy-to-use questionnaires, like the SRA-34, can support this process.

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Summary (English)

SUMMARY OF LITERATURE Patients with schizophrenia have a high burden of disease. Many of them suffer from co-morbid depressive symptoms, which may further increase the burden of disease. Depressive symptoms overlap with other symptoms of schizophrenia, which complicates the recognition of depressive symptoms by the clinician. Recognizing depressive symptoms is important for an optimal treatment strategy of these patients (e.g. by antidepressants). The first aim of this thesis is to optimize the screening and monitoring of depressive symptoms in clinical practice. We will focus on the patients' perspective by means of self-report. The second aim of this thesis is to describe the relationship between depressive symptoms and D_2 receptor affinity and occupancy.

SUMMARY OF CHAPTER 2-8 Antidepressants are frequently prescribed in patients with psychotic disorders, although their effectiveness is unclear in patients with schizophrenia. Chapter 2 describes the course of depressive symptoms in relation with prescribing patterns of antidepressants and identifies predictors for having persistent depressive symptoms. Depressive symptoms of a cohort of 214 patients with schizophrenia were rated by their clinician as part of annual routine outcome monitoring of the patients' health. We showed that depressive symptoms were prevalent among 43% of the patients and their symptoms persisted for more than half of these patients after one year of follow-up. Antidepressants were prescribed for 40% of the patients and the majority (57%) continued this therapy after one year. Multivariable analysis showed that for patients with depressive symptoms at baseline, polypharmacy was a potential risk factor to keep having depressive symptoms. Patients with more severe psychopathology had a higher risk to develop depressive symptoms the following year.

Chapter 3 is a systematic review of the literature on depression instruments with published measures of reliability and validity in patients with schizophrenia. Forty-eight publications described the performance of six depression instruments in patients with schizophrenia, including three depression instruments primarily developed for use in depressed populations and two depression subscales of psychotic symptom scales. The only depression instrument especially developed for the use in patients with schizophrenia was the Calgary Depression Scale for Schizophrenia (CDSS) interview. The CDSS outperformed other depression scales in this population, since it correlated well with other depression instruments (concurrent validity),

most accurately differentiated depressive symptoms from negative symptoms of schizophrenia (divergent validity) and was least likely to miss cases of depression or misdiagnose depression (predictive validity). We would recommend utilizing the CDSS interview for the measurement of depressive symptoms in research and in daily clinical practice of patients with schizophrenia.

Another outcome of Chapter 3 was the gap in the literature regarding self-report depression instruments with tested validity in patients with schizophrenia. The Beck Depression Inventory was the only self-report rating scale included for analysis, but its predictive validity was rather poor in this population. Chapter 4 and 5 evaluated the agreement of two other self-report depression scales with the CDSS interview that served as the gold standard for the measurement of depressive symptoms in patients with schizophrenia.

The Quick Inventory for Depressive Symptoms (QIDS-SR_{16}) is a quick and popular self-report depression instrument. Because its validity has not extensively been tested in patients with schizophrenia, Chapter 4 evaluated several aspects of reliability and validity of the QIDS-SR_{16} in 621 patients. Our study showed that patients were able to reliably rate their depressive symptoms using the QIDS-SR16. The QIDS-SR_{16} well discriminated depressive symptoms from negative symptoms, as rated by the Positive and Negative Syndrome Scale (PANSS). The QIDS-SR_{16} agreed, however, moderately with observed depressive symptoms by means of the CDSS. This moderate correlation suggests differences with the gold standard depression rating scale. The sedative effects of antipsychotics may have confounded the self-report of depressive symptoms by the QIDS-SR_{16}, while the CDSS is less sensitive to confounding by these antipsychotic side effects. We therefore advise against utilizing the QIDS-SR_{16} for the measurement of depressive symptoms in patients with schizophrenia.

In Chapter 5 we aimed to compare the outcome of the CES-D with the CDSS interview. As part of routine outcome monitoring by a Dutch mental health care center, 122 patients with schizophrenia completed the CES-D and the CDSS interview. As a result, the correlation between the total scores of the CES-D and the CDSS was 0.70. This good agreement with the gold standard for the assessment of depressive symptoms in patients with schizophrenia implies that self-rating of depression by means of the CES-D is adequate in this population. Furthermore, the Center for Epidemiologic Studies-Depression (CES-D) has a minimal number of items measuring symptoms

that overlap with negative symptoms, compared to other self-report depression instruments. Future research is needed to determine the predictive validity of the CES-D to detect cases of depression in patients with schizophrenia.
Depressive symptoms can be one of the side effects of antipsychotics. Chapter 6 investigated if patients attribute depressive symptoms to their antipsychotics, independent from other antipsychotic side effects. The main aim of this chapter was to develop a shorter version of the 74-item Subjects' Response to Antipsychotics (SRA) questionnaire, based on the latent structure of the SRA. A sample of 1478 patients with schizophrenia completed the SRA self-report questionnaire to assess their experiences in response to antipsychotics. Item reduction was based on factor loadings of the items and redundancy of the content of the items, as evaluated by an expert panel. Exploratory factor analysis of the SRA-74 identified fourteen factors, including one factor of depressive symptoms. This implied that the two depression items 'I feel down' and 'I feel more depressed' of the SRA-74 can be used to investigate the patients' attribution of depressive symptoms to antipsychotics. The number of items of the SRA was reduced by 12 because of unreliable factor loadings and 28 based on overlapping content, resulting in a 34-item version of the SRA. The clinician can use the SRA-34 as a quick checklist to evaluate the balance between desired and undesired effects of antipsychotics with the patient.

Depressive symptoms in response to antipsychotics have been associated with the action of antipsychotics on the dopamine D_2 receptor in the brain. Chapter 7 described the relationship between antipsychotic dose and occupancy of the D_2 receptor for a series of antipsychotics. We estimated the median D_2 receptor occupancy for a given antipsychotic dose, based on meta-analysis of published D_2 receptor occupancy data in patients with schizophrenia treated with antipsychotics. We included 51 studies, describing 606 patients for eight antipsychotics. Non-linear mixed effects models described the dose-occupancy relationship by Michealis Menten curves with narrow confidence bands around the therapeutic dose range. Maximum occupancy levels were estimated for haloperidol (91.9%), risperidone (92.4%), olanzapine (96.5%), clozapine (61.7%), quetiapine 49.1%), aripiprazole (86.9%), ziprasidone (82.9%) and amisulpride (85.0%). The total variability in observed occupancy values was high, which was mostly explained by inter-individual differences, next to a significant effect of heterogenenity between studies. In conclusion, these eight dose-occupancy curves can be used to estimate the median level of D_2 receptor occupancy of a population of patients with schizophrenia. These dose equivalents can help to compare different antipsychotics

and doses on D_2 receptor mediated side effects.

Chapter 8 focused on the relationship between depressive symptoms and antipsychotic type (affinity) or dose (occupancy). We investigated the effect of monotherapy and combinationtherapy on depressive symptoms in patients with schizophrenia, measured by SRA-questionnaire. Antipsychotic subtypes were classified by their affinity for the D_2 receptor, as partial (aripiprazole), weak (clozapine and quetiapine), medium (olanzapine) and high (haloperidol and risperidone). The patients' D_2 receptor occupancy was estimated using the dose-equivalents described in Chapter 7. Of the 1298 patients included, perceived a considerable number of 16% depressive symptoms as an antipsychotic side effect. Logistic regression analysis could not confirm an association between depressive symptoms and antipsychotic D_2 receptor affinity or the level of D_2 occupancy in patients using antipsychotic monotherapy. Patients using antipsychotic combination therapy (22%) were more likely to attribute depressive symptoms to their antipsychotics than patients using antipsychotic monotherapy (OR[95%CI] = 1.443[1.033 – 2.015]). The high cumulative doses prescribed for patients using antipsychotic combination therapy suggested a dose-response relationship between depressive symptoms and D_2 receptor occupancy. We would recommend being cautious with prescribing antipsychotic combination therapy to avoid drug-induced depressive symptoms.

OVERALL CONCLUSION Routine outcome monitoring in patients with schizophrenia revealed a high prevalence and persistence of depressive symptoms. Antidepressants are frequently prescribed and maintained in the treatment of depressive symptoms. In clinical practice, clinicians may have difficulties to adequately distinguish depressive symptoms from other psychotic symptoms in this population. The use of validated instruments like the Calgary Depression Scale for Schizophrenia (CDSS) aids the clinician in the recognition of depressive symptoms, and may thereby prevent over-recognition or over-treatment with antidepressants. The Center of Epidemiologic Studies-Depression scale (CES-D) is a promising self-report depression instrument that needs additional investigation in patients with schizophrenia.

Patients attribute depressive symptoms to their antipsychotics, independently from other experiences in response to antipsychotics. We developed the SRA-34 self-report questionnaire to evaluate whether the patient attributes depressive symptoms,

or other experiences, to their antipsychotics. Antipsychotic combination therapy has been associated with depressive symptoms, suggesting a relationship with excessive dopaminergic blockade. A dose-response relationship with D_2 receptor occupancy can however not be confirmed in patients using antipsychotic monotherapy, probably because of cautious dosing strategies. Still, the high inter-individual differences in occupancy values for a given antipsychotic dose underline the need for individual dosing strategies. Shared decision making between patient and clinician is an elegant strategy to address individual differences. Self-rating of experiences by short and easy-to-use questionnaires, like the SRA-34, support the patient in this process.

Samenvatting (Nederlands)

INLEIDING Schizofrenie is een psychische aandoening, waardoor iemand langdurig belemmerd kan worden in sociaal en maatschappelijk functioneren. Mensen met schizofrenie hebben last van waanideeën, of horen stemmen die er niet zijn. In deze thesis gaat het vaak over een brede groep patiënten met schizofrenie of een andere psychotische stoornis, waarnaar zal worden gerefereerd met 'patiënten met schizofrenie'. Naast de psychotische klachten, kunnen mensen met schizofrenie ook last hebben van depressieve klachten. De aard van depressieve klachten is vaak lastig te achterhalen, wat een effectieve behandeling in de weg kan staan. Depressieve symptomen lijken namelijk op andere symptomen die met schizofrenie gepaard gaan, zoals een afgevlakt gevoelsleven en sociale teruggetrokkenheid (negatieve symptomen). Ook is het niet uitgesloten dat depressieve symptomen een bijwerking zijn van de antipsychotica, waarmee de patiënten doorgaans worden behandeld. Daarnaast kan deze neerslachtigheid te maken hebben met een drastisch veranderd toekomstperspectief, ten gevolge van deze psychiatrische aandoening. Afhankelijk van de aard van de depressieve klachten, kunnen deze patiënten behandeld worden met antidepressiva, een aanpassing in de behandeling met antipsychotica, of gesprekstherapie.

SAMENVATTING HOOFDSTUK 2-8 Het is bekend dat antidepressiva veelvuldig worden voorgeschreven, ondanks dat er in de literatuur onduidelijkheid heerst over de effectiviteit van deze medicijnen bij patiënten met schizofrenie. Hoofdstuk 2 beschrijft het gebruik van antidepressiva door mensen met schizofrenie in relatie tot het beloop van depressieve symptomen over de tijd. Om dit te onderzoeken werden 214 patiënten met schizofrenie tweemaal gescreend op het hebben van depressieve symptomen, met een tussenliggende tijd van één jaar. Antidepressiva werden door 40% van de patiënten gebruikt en de meerderheid bleef deze medicatie na één jaar doorgebruiken. Toch vertoonde bijna de helft van de patiënten depressieve symptomen, die bij het merendeel ook het volgende jaar aanhielden. Opvallend was dat hoe meer medicijnen een patiënt naast elkaar gebruikte, hoe kleiner de kans op een verbetering van depressieve symptomen was. Van de patiënten die eerder geen depressieve symptomen hadden, ontwikkelde één op de vijf patiënten het opvolgende jaar wel depressieve symptomen. Daarvan liepen patiënten met een ernstig ziektebeeld extra risico om depressieve symptomen te ontwikkelen. Wij zouden willen adviseren om depressieve klachten bij deze patiënten nauwlettend te volgen, met name bij patiënten met een ernstig ziektebeeld en/of die veel medicijnen tegelijk gebruiken.

Depressie instrumenten kunnen de clinicus helpen om depressieve symptomen te herkennen. Deze instrumenten kunnen zowel interviews betreffen, als vragenlijsten die de patiënt zelf in kan vullen. Om de clinicus te helpen bij het kiezen van een geschikt meetinstrument, geeft Hoofdstuk 3 een overzicht van depressie instrumenten die toepasbaar zijn bij patiënten met schizofrenie. Op basis van systematisch literatuuronderzoek hebben we alleen díe depressie instrumenten geselecteerd voor evaluatie, waarvan een breed scala aan gegevens over de betrouwbaarheid en validiteit in patiënten met schizofrenie bekend was. In totaal vonden we 48 publicaties die de eigenschappen van zes depressie instrumenten in patiënten met schizofrenie beschreven. Het enige depressie instrument dat speciaal ontwikkeld was om depressieve symptomen bij mensen met schizofrenie te meten was het Calgary Depression Scale for Schizophrenia (CDSS) interview. De overige instrumenten waren ontwikkeld voor patiënten met depressie of depressie-subschalen van instrumenten die de ernst van de psychotische symptomen meten. Het CDSS interview maakte het best onderscheid tussen depressieve symptomen en negatieve symptomen van schizofrenie (divergente validiteit) en voorspelde een diagnose van depressie het best ten opzichte van andere depressie instrumenten bij mensen met schizofrenie (voorspellende validiteit). Op basis van deze resultaten zouden wij willen aanbevelen het CDSS interview te gebruiken om depressieve symptomen te herkennen in de behandeling van mensen met schizofrenie.

Een andere uitkomst van het literatuur onderzoek was het gebrek aan valide zelfinvul vragenlijsten voor patiënten met schizofrenie. De enige zelfinvul vragenlijst die we hebben geëvalueerd was de Beck Depression Inventory (BDI), maar de voorspellende validiteit van dit instrument was matig. In Hoofdstuk 4 en 5 hebben de twee andere zelfinvul vragenlijsten (QIDS-SR_{16} en CES-D), die nog niet uitvoerig getest waren bij patiënten met schizofrenie, vergeleken met het CDSS interview. De CDSS werd hierbij beschouwd als de gouden standaard voor het meten van depressieve symptomen bij schizofrenie.

Het doel van Hoofdstuk 4 was te toetsen of patiënten met schizofrenie met behulp van de Quick Inventory for Depressive Symptoms (QIDS-SR_{16}) op een betrouwbare en valide manier de ernst van hun depressieve symptomen zelf kunnen rapporteren. De 621 deelnemers vulden QIDS-SR_{16} in en werden ter vergelijking geïnterviewd met de CDSS over depressieve symptomen en met de Positive and Negative Syndrome Scale (PANSS) over hun negatieve symptomen. Op basis van correlaties werd de samenhang

tussen de totaalscores van deze instrumenten vergeleken. Ondanks dat de QIDS-SR_{16} genoeg onderscheid maakte met negatieve symptomen (PANSS), was er een matige overeenkomst tussen de QIDS-SR_{16} en de geobserveerde depressieve symptomen volgens de CDSS. Een mogelijke verklaring voor het verschil met de CDSS is de manier waarop veranderingen in slaap- en eetpatroon worden gemeten door de QIDS-SR_{16}. De samenhang tussen het gebruik van antipsychotica met een hoge affiniteit voor de histamine receptor en de hoge QIDS-SR_{16} scores op vragen over toegenomen slaap en eetlust, impliceerde dat de QIDS-SR_{16} gevoelig is voor verstoring door sedatieve bijwerkingen van antipsychotica. Op basis van bovengenoemde resultaten zouden we zelf-rapportage van depressieve symptomen met de QIDS-SR_{16} vragenlijst willen afraden bij mensen met schizofrenie.

Het doel van Hoofdstuk 5 was om de ernst van de depressieve symptomen zoals gemeten met de Center for Epidemiologic Studies-Depression (CES-D) te vergelijken met de uitkomst van het CDSS interview. Daartoe werden 122 patiënten in zorg bij GGZ Drenthe gevraagd om de CES-D in te vullen en geïnterviewd te worden met de CDSS. De ernst van depressieve symptomen zoals gemeten met de CES-D kwam goed overeen met de CDSS (correlatie 0.70). De resultaten wijzen uit dat zelf-rapportage met behulp van de CES-D van depressieve symptomen een geschikte manier kan zijn om depressieve symptomen te meten bij patiënten met schizofrenie. Bovendien lijken de depressieve symptomen die worden gemeten met de CES-D minimaal te overlappen met negatieve symptomen en bijwerkingen van antipsychotica, in vergelijking met andere depressie meetinstrumenten. Vervolgonderzoek zal echter wel nodig zijn om te bepalen of de CES-D depressie voldoende goed kan voorspellen in deze patiëntengroep.

Depressieve symptomen kunnen een bijwerking zijn van antipsychotica. In Hoofdstuk 6 onderzochten we of patiënten depressieve symptomen als een apart type bijwerking zien, of dat deze symptomen zich alleen samen voordoen met andere bijwerkingen van antipsychotica (bijv. afgevlakt gevoel en extrapyramidale bijwerkingen). Het hoofddoel van dit onderzoek was het inkorten van een lange vragenlijst over ervaringen met antipsychotica. Een groep van 1478 patiënten met schizofrenie werd gevraagd de 74 vragen van de Subjects' Reactie op Antipsychoticagebruik (SRA-74) vragenlijst in te vullen, om te onderzoeken welke ervaringen ze toeschreven aan antipsychotica. Met behulp van factor analyse werd de samenhang tussen de ervaringen met antipsychotica weergegeven, wat tevens de basis vormde voor de verkorte versie

van de SRA-74. Het bleek dat de SRA-74 uit 14 verschillende onderwerpen bestond, waaronder één specifiek over depressieve symptomen. Het bestaan van de aparte 'factor' over depressieve symptomen (i.e. de vragen 'door antipsychotica voel ik me depressiever / meer down'), impliceerde dat deze twee SRA-vragen valide kunnen worden ingezet om depressieve symptomen in reactie op antipsychoticagebruik te onderzoeken. Daarnaast bleek dat een deel van vragen niet kon worden gegroepeerd onder één van de 14 onderwerpen. Deze vragen waren blijkbaar te weinig specifiek en indien ook niet klinisch relevant geacht volgens het expert panel was besloten om deze vragen weg te laten in de verkorte versie. Dit resulteerde in een vragenlijst van 34 vragen, waarmee de balans tussen gewenste en ongewenste effecten van antipsychotica met de patiënt kan worden geëvalueerd.

Depressieve symptomen kunnen gerelateerd zijn aan de mate waarin antipsychotica de dopamine D_2 receptoren bezetten in de hersenen. Om antipsychotica te kunnen vergelijken in hun effect op depressieve symptomen ontwikkelden we in Hoofdstuk 7 een serie dosisequivalenten, die het verband tussen dosis en D_2 receptorbezetting beschrijven voor de vaakst voorgeschreven antipsychotica. Op basis van gepubliceerde gegevens uit hersenscans van mensen die antipsychotica gebruiken, schatten we de gemiddelde D_2 receptorbezetting door antipsychotica (meta-analyse). We vonden 51 artikelen die voor in totaal 606 patiënten de D_2 receptorbezetting beschreven. Hieruit konden we voor acht antipsychotica de relatie tussen dosis en D_2 receptorbezetting met een curve beschrijven. Daaruit volgde dat de maximaal haalbare D_2 receptorbezetting per antipsychoticum was: haloperidol (91.9%), risperidone (92.4%), olanzapine (96.5%), clozapine (61.7%), quetiapine 49.1%), aripiprazole (86.9%), ziprasidone (82.9%) en amisulpride (85.0%). Opmerkelijk was dat de D_2 receptorbezetting sterk varieerde tussen patiënten, maar ook tussen studies. De verschillen tussen studies konden niet verklaard worden door de beeldvormende techniek die werd gebruikt; mogelijk speelden andere methodologische aspecten hier een rol in. Leeftijd noch geslacht leken de verschillen tussen patiënten te verklaren; misschien dat individuele verschillen in metabolisme hieraan ten grondslag liggen. Hierdoor zijn de curves niet geschikt om de D_2 receptorbezetting voor een individuele patiënt te schatten. Desondanks gaven de betrouwbaarheidsintervallen van de curves aan dat de gemiddelde D_2 receptorbezetting wel nauwkeurig kan worden geschat voor een groep patiënten. Onze dosisequivalenten kunnen worden gebruikt om effecten van antipsychotica op het dopaminerge systeem van patiënten te vergelijken tussen antipsychotica en doseringen.

In Hoofdstuk 8 is beschreven of de relatie tussen depressieve symptomen gerelateerd is aan een bepaald type antipsychoticum en/of dosering. We vergeleken de relatie met depressieve symptomen tussen zes antipsychotica, gerangschikt naar de mate van binding aan de dopamine D_2 receptor. De relatie met de dosering werd onderzocht door de voorgeschreven dosis antipsychoticum om te zetten naar een evenredige maat van D_2 receptorbezetting in de hersenen. Met behulp van de SRA vragenlijst werden patiënten gevraagd of zij depressieve symptomen toeschreven aan hun antipsychotica gebruik. Van de 1298 patiënten die onderzocht werden, schreef 16% depressieve symptomen toe aan antipsychotica gebruik. Analyse met logistische regressie analyse kon echter geen verband tussen depressie symptomen en een bepaald type antipsychotica, of mate van D_2 receptorbezetting aantonen. Opvallend was wel dat patiënten die een combinatie van antipsychotica gebruikten een verhoogd risico hadden op depressieve symptomen, vergeleken met patiënten die één antipsychoticum gebruikten. De totale dosis van patiënten met combinatietherapie was hoog, waardoor een dosis-effect relatie tussen D_2 receptorbezetting en depressieve symptomen niet geheel uitgesloten kan worden. Op basis van dit onderzoek kunnen we echter geen aanbeveling doen voor een preferent type antipsychoticum of dosering. We zouden de clinicus wel willen adviseren om voorzichtig te zijn met het voorschrijven van een combinatie van antipsychotica, ter voorkoming van bijkomstige depressieve symptomen.

SLOTWOORD Jaarlijkse screening wees uit dat depressieve symptomen vaak voorkomen en persisteren bij mensen met schizofrenie, ondanks dat antidepressiva veelvuldig en langdurig worden voorgeschreven. De resultaten benadrukten het belang van gedegen vervolgonderzoek naar de effectiviteit van antidepressiva, maar ook naar alternatieve behandelstrategieën van depressieve klachten bij patiënten met schizofrenie.

In praktijk kan het voor de psychiater moeilijk zijn om depressieve symptomen te onderscheiden van andere psychotische symptomen, zoals negatieve symptomen. Het gebruik van gevalideerde instrumenten zoals de Calgary Depression Scale for Schizophrenia (CDSS) kan de psychiater helpen om depressieve symptomen beter te herkennen. Hiermee kan mogelijk overdiagnostiek en overbehandeling met antidepressiva worden voorkomen. De Center of Epidemiologic Studies-Depression (CES-D) zelf-invul vragenlijst kan een geschikt alternatief zijn voor het meten van

depressieve symptomen, ook al zou een definitieve aanbeveling voor het gebruik van de CES-D bij mensen met schizofrenie moeten blijken uit vervolgonderzoek.

Patiënten schreven depressieve symptomen vaak toe aan het gebruik van antipsychotica. Deze depressieve symptomen leken onafhankelijk van andere bijwerkingen van antipsychotica. Onze bevinding dat combinatietherapie van antipsychotica was gerelateerd aan depressieve symptomen suggereerde een relatie met overmatige blokkade van het dopamine systeem. Echter konden we geen dosis-effect relatie aantonen met D_2 receptorbezetting bij patiënten die één antipsychoticum tegelijk gebruikten, mogelijk omdat deze antipsychotica in nette doseringen werden voorgeschreven. De grote verschillen in D_2 receptorbezetting tussen patiënten voor een gegeven dosering benadrukten het belang van een individuele aanpak bij het instellen op antipsychotica. Een manier om de individuele behoeften van de patiënt tegemoet te komen is gezamenlijke besluitvorming. De SRA-34 vragenlijst kan helpen om patiënten systematisch hun ervaringen met antipsychotica te laten rapporteren. Door het hanteren van deze korte en gebruiksvriendelijke vragenlijst kan de patiënt nog beter gehoord worden, en daarmee de kwaliteit van de zorg verbeterd worden.

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DANKWOORD

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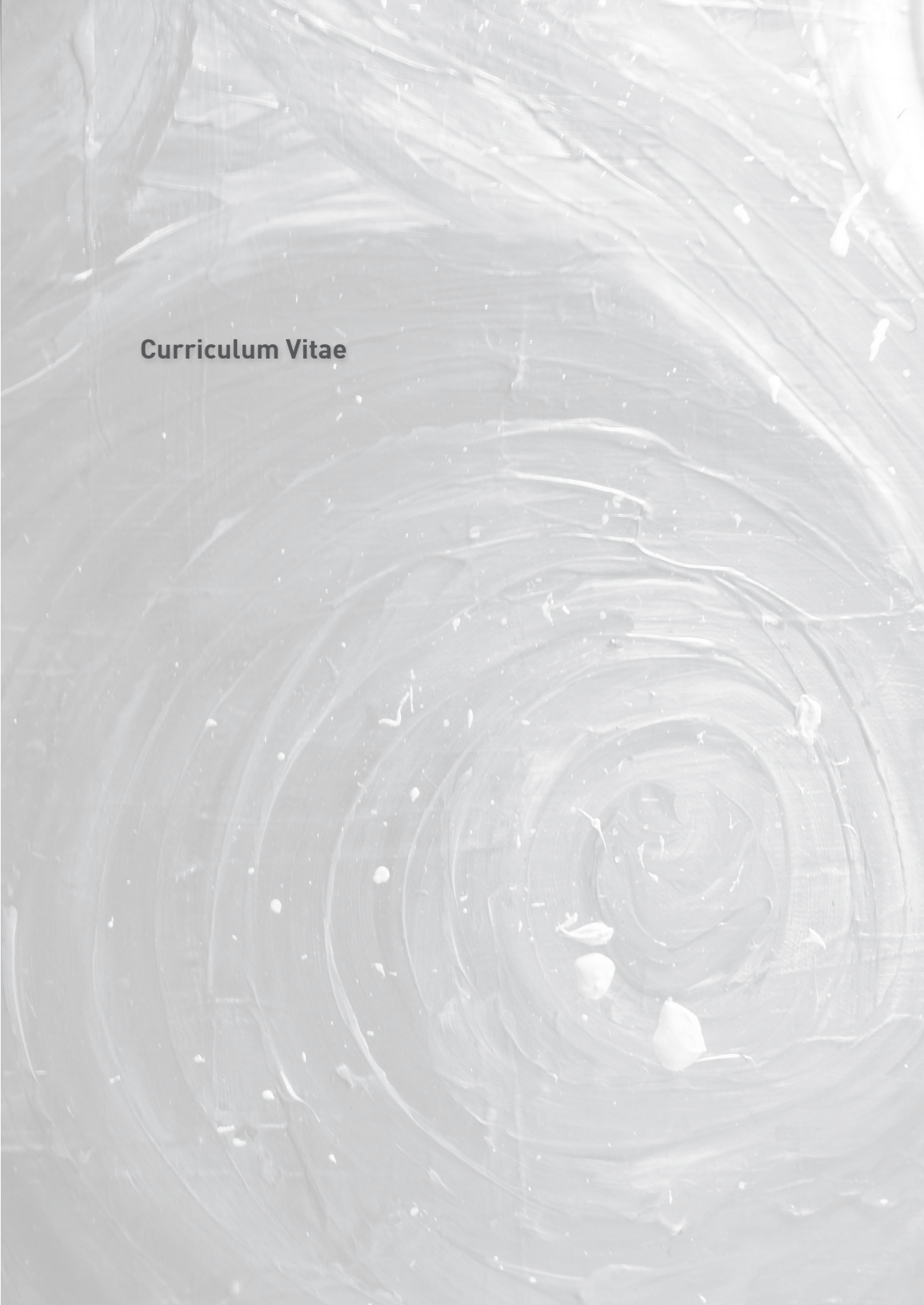
SLOTWOORD Ik beschouw het als een groot voorrecht dat ik mee heb mogen werken aan de verbetering van de gezondheidszorg voor deze kwetsbare groep mensen en wil alle betrokkenen succes wensen met de voortzetting van dit werk.



Curriculum Vitae

CURRICULUM VITAE

Irene Mathilde Lako was born at Januari 20th 1984 in Den Haag, The Netherlands. She was raised in Alkmaar, where she graduated at the Murmellius Gymnasium in 2002. After finishing the interdisciplinary 'Beta-Gamma' trajectory in her first year at the University of Amsterdam, she proceeded with Bio-medical Sciences. In a nine month internship at Solvay Pharmaceuticals, she developed a new variant of a popular animal model for negative symptoms of schizophrenia. During her second internship at the Netherlands Institute for Neuroscience, she studied the effects of sleep deprivation on cognition. In 2007 she graduated as neurobiologist at the University of Amsterdam. Subsequently, she started her career in clinical research at the University Medical Center in Groningen. She facilitated the implementation of the PHArmacotherapy Monitoring and OUtcome Study (PHAMOUS) in the North of the Netherlands, where she trained research nurses to screen patients with psychotic disorders on their mental and physical health. In 2009 she joined the department of Pharmacotherapy and Pharmaceutical Care (University of Groningen) as PhD Candidate. She used to combine these activities with marathon ice speed skating in the national competition. The SHARE Research School gave her the opportunity to gain experience in various aspects of biomedical statistics and psychiatric epidemiology. She is currently employed as Medical Writer at Pharmaceutical Research Associates Inc. (PRA), located in Groningen, The Netherlands.

Appendix 1

Subjects Response to Antipsychotics – 34
Questionnaire

SRA-34
Subjects Response to Antipsychotics

Short version (English)

Brief questionnaire to evaluate desired and undesired effects of antipsychotics

I.M. Lako
H.A. Wolters
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BACKGROUND INFORMATION

Date: .....

What is your sex?

1. Male 0
2. Female 0

What is your age?

..... Years

What is your current civil status?

1. Married 0
2. Living together 0
3. Single 0
4. Divorced 0
5. Widow / widower 0
6. Other relationship 0

Which education did you complete?

1. None 0
2. Primary school 0
3. Secondary school 0
4. Technical college 0
5. Higher National Diploma 0
6. University 0
7. Other 0

If you know which illness(es) you, according to the doctor, suffer from, state this below.

1.....
2.....
3.....

If you know the names and dosage of the medicine you take, please state this below

dose

1..... - .....
2..... - .....
3..... - .....
4..... - .....
5..... - .....

During which period of time have you been taking your current antipsychotic medicine?

1. Less than 1 month 0
2. Between 1 and 3 months 0
3. Between 3 and 12 months 0
4. Between 1 and 2 years 0
5. More than 2 years 0

How do you take the antipsychotic medicine?

1. Oral (pills) 0
2. Depot (injection) 0

Do you take the medication as prescribed?

1. I mostly take the medication as prescribed 0
2. I miss taking the antipsychotic medicine a few times a month 0
3. I miss taking the antipsychotic medicine a few times a week 0
4. I never take the antipsychotic medicine 0

APPENDIX 1

INTRODUCTION

This questionnaire consists of experiences one could have when one takes antipsychotic medicine. The question is whether you have had this experience during the past week due to the antipsychotic medication. At the end of the questionnaire there are three concluding questions. There are no correct or incorrect answers, it's your own opinion that counts.

Example:

Due to the antipsychotic medication:

1. I can think more clearly

If, during the past week, you have had the idea to a high degree that you think more clearly due to the
antipsychotic medication, then the answer is: '*yes, to a high degree*'.

If, during the past week, you have had the idea that to a certain degree you think more clearly due to
the antipsychotic medication, then the answer is: '*yes, to a certain degree*'.

If, during the past week, you haven't had the idea that you think more clearly due to the antipsychotic
medication, then the answer is: '*no*'.

Attention!

If, during the past week, you have had the idea that you think more clearly, but that it's not due to the antipsychotic medication, then the answer is also '*no*'.

		No	Yes, to a certain degree	Yes, to a high degree	
	Due to the antipsychotic medication:				
1	My emotions are dull	0	0	0	EF
2	I feel happier	0	0	0	RA
3	My weight has increased	0	0	0	WA
4	I have less energy for socializing	0	0	0	SW
5	I can't remember well	0	0	0	SD
	Due to the antipsychotic medication:				
6	I react more slowly	0	0	0	SD
7	I am less anxious	0	0	0	RP
8	I feel more depressed	0	0	0	DS
9	I am constipated more often	0	0	0	OU
10	I can concentrate better	0	0	0	RA
	Due to the antipsychotic medication:				
11	I leak urine more often	0	0	0	OU
12	My vision is more blurred	0	0	0	OU
13	I have more trouble sitting still	0	0	0	OU
14	I hear fewer voices	0	0	0	RP
15	It is more difficult for me to have an orgasm	0	0	0	SP
	Due to the antipsychotic medication:				
16	I have a dry mouth more often	0	0	0	OU
17	My memory has improved	0	0	0	RA
18	I have more tremors	0	0	0	EP
19	I have more interest in my surroundings	0	0	0	RS
20	I am nauseous more often	0	0	0	OU
	Due to the antipsychotic medication:				
21	My sex drive has decreased	0	0	0	SP
22	I am dizzy more often	0	0	0	OU
23	Dealing with others is easier	0	0	0	RS
24	I can think more clearly	0	0	0	RC
25	I get physically tired more easily	0	0	0	SW

		No	Yes, to a certain degree	Yes, to a high degree	
	Due to the antipsychotic medication:				
26	I have more difficulty waking up	0	0	0	IS
27	I am less creative	0	0	0	OU
28	My muscles are more stiff	0	0	0	EP
29	I have more control over my thoughts	0	0	0	RC
30	I have increased salivation	0	0	0	OU
	Due to the antipsychotic medication:				
31	I have more trouble concentrating	0	0	0	SD
32	I have an increased appetite	0	0	0	WA
33	I can sleep better	0	0	0	RIS
	For females only:				
34	I menstruate less often	0	0	0	OU
	Concluding questions:				
C1	I am satisfied with the antipsychotic medication	0	0	0	C
C2	I feel dependent on antipsychotic medication in order to function	0	0	0	C
C3	The advantages of antipsychotic medication outweigh the disadvantages	0	0	0	C

Thank you for your response. Below you can state any other experiences with antipsychotic medication, desired or undesired:

LEGEND. SRA-34 subscales (item number)

Undesired effects

WA Weight & Appetite (3,32)
IS Increased Sleep (26)
SP Sexual Problems (15,21)
SW Social Withdrawal (4,25)
SD Slowed Down (5,6,31)
EF Emotional Flattening (1)
EP EPS (18,28)
DS Depressive Symptoms (8)
OU Other Undesired effects (9,11,12,13,16,20,22,27,30,34)

Desired effects

RP Recovery Psychosis (7,14)
RC Recovery Cognition (24,29)
RS Recovery Social (19,23)
RA Recovery Attention (2,10,17)
RIS Recovery Increased Sleep (33)

Appendix 2

Subjects Reactie op Antipsychoticagebruik – 34
Vragenlijst

SRA-34
Subjects Reactie op Antipsychoticagebruik

Verkorte versie (Nederlands)

Vragenlijst voor de evaluatie van gewenste en ongewenste effecten van antipsychotica gebruik

I.M. Lako
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ACHTERGRONDGEGEVENS

Datum: .....

Wat is uw geslacht?

1. Man 0
2. Vrouw 0

Wat is uw leeftijd?

..... Jaar

Wat is uw huidige samenlevingsvorm?

1. Gehuwd 0
2. Samenwonend 0
3. Alleen wonend 0
4. Wettelijk gescheiden 0
5. Weduwe/ weduwnaar 0
6. Overige relaties 0

Welke schoolopleiding heeft u afgemaakt?

1. Geen 0
2. Lagere school 0
3. Middelbare school 0
4. Middelbaar Beroepsonderwijs 0
5. Hoger Beroepsonderwijs 0
6. Universiteit 0
7. Anders 0

Als u weet welke ziekte(s) u volgens de arts lijdt, geef dit hieronder aan.

1.....
2.....
3.....

Als u de namen en de dosering weet van de medicijnen die u gebruikt, wilt u dat hieronder aangeven.

dosis

1..... - .....
2..... - .....
3..... - .....
4..... - .....
5..... - .....

Hoe lang gebruikt u gedurende uw gehele leven antipsychotische medicijnen?

1. Minder dan 1 maand 0
2. Tussen 1 en 3 maanden 0
3. Tussen 3 en 12 maanden 0
4. Tussen 1 en 2 jaar 0
5. Meer dan 2 jaar 0

Hoe gebruikt u de antipsychotische medicijnen?

1. Oraal (pillen) 0
2. Depot (injectie) 0

Bent u trouw in het innemen van de medicatie?

1. Ik neem meestal trouw in 0
2. Ik neem enkele keren per maand de antipsychotische medicijnen niet in 0
3. Ik neem de antipsychotische medicijnen enkele keren per week niet in 0
4. Ik neem nooit de antipsychotische medicijnen in 0

INLEIDING

Deze vragenlijst bestaat uit ervaringen die mensen kunnen hebben als ze antipsychotische medicijnen gebruiken. De vraag is of u deze ervaringen de afgelopen week door de antipsychotische medicijnen heeft gehad. Aan het eind van de vragenlijst staan drie afsluitende vragen. Er zijn geen goede of foute antwoorden, het gaat om uw eigen mening.

Voorbeeld:

Door de antipsychotische medicijnen:

1. Denk ik helderder

Als u de afgelopen week het idee heeft dat u in sterke mate helderder denkt door de antipsychotische medicijnen dan is het antwoord: '*ja, in sterke mate*'.

Als u de afgelopen week het idee heeft dat u in enige mate helderder denkt door de antipsychotische medicijnen dan is het antwoord: '*ja, in enige mate*'.

Als u de afgelopen week het idee heeft dat u niet helderder denkt door de antipsychotica medicijnen dan is het antwoord: '*nee*'.

LET OP:

Als u de afgelopen week het idee heeft dat u *wel* helderder denkt, maar dat het *niet* komt door de antipsychotische medicijnen, dan is het antwoord ook '*nee*'.

		Nee	Ja, in enige mate	Ja, in sterke mate	
	Door de antipsychotische medicijnen:				
1	Zijn mijn emoties afgevlakt	0	0	0	EF
2	Voel ik mij opgewekter	0	0	0	RA
3	Is mijn gewicht toegenomen	0	0	0	WA
4	Heb ik minder energie voor sociale contacten	0	0	0	SW
5	Kan ik minder goed onthouden	0	0	0	SD
	Door de antipsychotische medicijnen:				
6	Reageer ik trager	0	0	0	SD
7	Ben ik minder angstig	0	0	0	RP
8	Voel ik me depressiever	0	0	0	DS
9	Zijn mijn darmen vaker verstopt	0	0	0	OU
10	Kan ik mij beter concentreren	0	0	0	RA
	Door de antipsychotische medicijnen:				
11	Verlies ik vaker urine	0	0	0	OU
12	Zie ik waziger	0	0	0	OU
13	Kan ik moeilijker stil zitten	0	0	0	OU
14	Heb ik minder stemmen	0	0	0	RP
15	Heb ik meer moeite om een orgasme te krijgen	0	0	0	SP
	Door de antipsychotische medicijnen:				
16	Heb ik vaker een droge mond	0	0	0	OU
17	Is mijn geheugen beter	0	0	0	RA
18	Tril ik meer	0	0	0	EP
19	Heb ik meer belangstelling voor mijn omgeving	0	0	0	RS
20	Ben ik vaker misselijk	0	0	0	OU
	Door de antipsychotische medicijnen:				
21	Heb ik minder behoefte aan seks	0	0	0	SP
22	Voel ik me vaker duizelig	0	0	0	OU
23	Is het omgaan met anderen makkelijker	0	0	0	RS
24	Kan ik helderder denken	0	0	0	RC
25	Voel ik me eerder lichamelijk vermoeid	0	0	0	SW

		Nee	Ja, in enige mate	Ja, in sterke mate	
	Door de antipsychotische medicijnen:				
26	Heb ik meer moeite met wakker worden	0	0	0	IS
27	Is mijn creativiteit verminderd	0	0	0	OU
28	Heb ik stijvere spieren	0	0	0	EP
29	Heb ik meer controle over mijn gedachten	0	0	0	RC
30	Heb ik meer speeksel in mijn mond	0	0	0	OU
	Door de antipsychotische medicijnen:				
31	Kan ik mij minder goed concentreren	0	0	0	SD
32	Heb ik meer eetlust	0	0	0	WA
33	Kan ik beter slapen	0	0	0	RIS
	Alleen voor vrouwen:				
34	Ben ik minder vaak ongesteld	0	0	0	OU
	Afsluitende vragen				
C1	Ik ben tevreden over de antipsychotische medicijnen	0	0	0	C
C2	Voor mijn functioneren voel ik me afhankelijk van de antipsychotische medicijnen.	0	0	0	C
C3	De voordelen van de antipsychotische medicijnen wegen op tegen de nadelen	0	0	0	C

Bedankt voor het invullen. Overige opmerkingen:

LEGENDA. SRA-34 subschalen (item number)

Ongewenste effecten

WA Weight & Appetite (3,32)
SP Sexual Problems (15,21)
SD Slowed Down (5,6,31)
EP EPS (18,28)
OU Other Undesired effects (9,11,12,13,16,20,22,27,30,34)
IS Increased Sleep (26)
SW Social Withdrawal (4,25)
EF Emotional Flattening (1)
DS Depressive Symptoms (8)

Gewenste effecten

RP Recovery Psychosis (7,14)
RC Recovery Cognition (24,29)
RS Recovery Social (19,23)
RA Recovery Attention (2,10,17)
RIS Recovery Increased Sleep (33)

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